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### THE THIRTY-THIRD MAUDSLEY LECTURE: TRENDS IN CHILD-PSYCHIATRY\*

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Too deeply moved to search for originality of expression, I hope that you will allow me to fall back on some of the well-worn phrases in acknowledging the honour conferred on me when I was chosen to be this year's Maudsley lecturer. My reaction was summarized in my reply to the notice which reached me in May, 1957. I wrote: "I accept amidst an understandable struggle between pride and humility. The name 'Maudsley Lecture' has an almost hallowed connotation among my professional contemporaries, and this invitation comes to me as a sort of crowning acme of my career." I am delighted to share my laurels with the Johns Hopkins University, which I joined exactly thirty years ago at the call of Adolf Meyer, whose gigantic contributions to psychiatric theory and practice were attested by the Royal Medico-Psychological Association when he was nominated to be the fourteenth Maudsley Lecturer in 1933. In going over the list of my illustrious predecessors in this series of addresses, beginning with Sir James Crichton Browne and Sir Frederick Mott, I find that I am the second United States psychiatrist to receive so great a distinction. I am certain that I voice the sentiments of my University when I say that it considers this event as an added and happily displayed feather in its richly decorated cap. The Johns Hopkins University has recognized the growing importance of child psychiatry by creating a full professorship in this discipline, and I am pleased to be the symbol of this recognition. And now your Association has indicated its desire that I speak as a child psychiatrist "as this specialty has not been covered in a Maudsley Lecture before". To have been selected as the first spokesman for child psychiatry in this group is a thrilling experience laden with heavy responsibilities.

The weight of these responsibilities produced in me quite a bit of anxious stirring from the moment when I began to gear myself for the decision on a suitable topic. Would it, I asked myself, be wise to bracket out a particular issue and elaborate it in some detail? This I and many others have done on frequent occasions, thus carrying together and trying to put in their proper

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places the numerous bricks which help to make up the total structure. But then it occurred to me that, instead, the occasion might serve me and my audience as a kind of pause for reflection about the nature of the structure itself. I turned for advice to two colleagues for whose wisdom and judgment I have the utmost admiration. John C. Whitehorn felt that a broad review of the field would be in order. Aubrey Lewis thought in terms of emphasis on the historical background of the specialty. Thus strengthened in my ripening preference for an overall discussion, I remembered a presentation which my one-time co-worker, your Kenneth Cameron, gave in 1955 as Chairman of the Child Psychiatry Section of this Association. It was a succinct outline of "past and present trends in child psychiatry". Cameron's brief and meaty address clinched my determination to dwell with you at some length on the evolution and scope of what now is known as child psychiatry.

In the light of present-day usage, it sounds incredible that the term child psychiatry itself had not acquired formal citizenship in the realm of professional or any other parlance until a little less than three decades ago. In the early 1930's, Tramer introduced it in its German form, *Kinderpsychiatrie*, as part of the name of the journal which he founded and which he has so capably edited throughout the years. In 1935, I chose *Child Psychiatry* as the title of my textbook. In 1937, at the initiative of Heuyer, an international congress in Paris, called together under the heading of *Psychiatrie infantile*, voted, not without opposition, to give legitimate status to the term. In 1938, finally, Schröder could proclaim that this name "has apparently become conventional in most civilized countries".

In a way, these baptismal quandaries and their comparatively recent resolution tell the story—a story which goes beyond a mere exercise in semantic niceties—of the origins of a branch of science which has become a respectable ingredient of our contemporary cultural milieu. I venture to say that child psychiatry and the name by which it goes today have arrived on the scene at approximately the same time. I am ready to defend the thesis that prior to the 1920's there was no body of knowledge or of clinical practice integrated enough to merit being set aside as an organized specialty.

Child psychiatry is the result of the convergence of a number of interests which for about half a century have existed alongside each other, with only sporadically and tenuously maintained areas of mutual contact. So long as these interests remained separated and confined to narrowly delimited spheres of activity, they each no doubt afforded highly significant insights which then, however, were applicable solely or principally within the constricted range in which the observations had been made. It was not until they could be brought together in one place that the edifice of child psychiatry could be erected as a comfortable dwelling unit with interconnecting rooms where a family of scientists could indulge in a fruitfully collaborative exchange of ideas and cognitions. Child psychiatry, in brief, is a fusion of what used to be a collection of more or less loosely scattered segments.

With your indulgence, I should like to have some of these segments pass in parade before you. It would seem reasonable to let psychiatry take the lead.

In the second half of the nineteenth century, several texts were published on "psychic disorders", "mental diseases", or "insanity" of children. Behavioural deviations interested Emminghaus (1887), Moreau de Tours (1888), Ireland (1898), and Manheimer (1899) chiefly as they seemed to fit diagnoses in accordance with classifications devised for adults. There was a tendency toward fatalism which saw in the reported disorders the irreversible results of



heredity, degeneracy, excessive masturbation, overwork, or religious preoccupation. These texts, nevertheless, offered a wealth of illustrative case material, no matter how sketchily some of it was presented in the form of anecdotal snapshots.

But let it not be said that the psychiatrists of that era were satisfied to be merely the mechanical recorders of observed or quoted instances. In the refreshing vigour of expanded curiosities, we sometimes, paying half-hearted homage to the psychiatric leaders of the past—and not too remote a past at that—are inclined to dismiss their formulations as obsolete relics, of consequence only to the medical historian. Those men certainly did pay attention to, and did try to find explanations for, psychotic manifestations in childhood, the very existence of which was questioned or even denied by many in the early part of this century. No more fitting example can be offered than that of Henry Maudsley in whose honour this series of annual lectures is held. In his *Physiology and Pathology of Mind*, published in 1867, Maudsley included a 34-page chapter on "Insanity of Early Life". In it, he not only attempted to correlate symptomatology with the patient's developmental status at the time of onset but also suggested an elaborate seven-point classification of the infantile psychoses. Anyone superciliously critical of either the terminology or the intrinsic cohesion of the grouping may well be reminded that the classification of the childhood psychoses is to this day a matter of controversial floundering.

Maudsley, as you know, rewrote his book a number of times. I cannot refrain from reproducing the introductory paragraph of the chapter on children in the revision of 1880. He began:

"How unnatural! is an exclamation of pained surprise which some of the more striking instances of insanity in young children are apt to provoke. However, to call a thing unnatural is not to take it out of the domain of natural law, notwithstanding that when it has been so designated it is sometimes thought that no more needs to be said. Anomalies, when rightly studied, yield rare instruction; they witness and attract attention to the operation of hidden laws or of known laws under new and unknown conditions; and so set the inquirer on new and fruitful paths of research. For this reason it will not be amiss to occupy a separate chapter with a consideration of the abnormal phenomena of mental derangement in children."

The "abnormal phenomena of mental derangement" continued for some time to be the almost exclusive interest which academic psychiatry had for children. This type of preoccupation found its culmination in the second edition of Ziehen's treatise on the mental diseases (*Geisteskrankheiten*) of childhood which appeared as late as in 1925. Unparalleled as a reference book and as an exhaustive bibliographic guide, it started out with this categorical statement: "For childhood the same division of psychoses is recommended as for the later ages, namely (a) psychoses *with* intellectual defect and (b) psychoses *without* intellectual defect." Ziehen's book was, indeed, on the whole an almost literal translation of adult psychiatry into terms of how much of it one might find in children. The author must have proceeded in about the following manner: "My readers are, of course, familiar with paranoia, melancholia, hebephrenia, stupor, hysteria, etc., in adults; now let us see how frequently these things are seen in children and how similarly or dissimilarly they manifest themselves." Abnormalities of the cortical structure and constitutional predisposition were considered as the dominant aetiological factors.

An avowed emphasis on an organic and genetic background prevailed also in Sancte de Sanctis' *Neuropsychiatria infantile*, published in the same year as



Ziehen's book. De Sanctis, scorning the modern direction toward "clinical individualism", complained that "the study of individual differences causes some to lose the aspect of group characteristics" and that "the investigation of intimate psychodynamics distracts the view of others from the inevitable play of its nervous or, more generally, vital partner". He went to the other extreme of losing sight of personality because of his strict adherence to somatic and localizing preoccupations.

This summary completes the psychiatric vanguard of the procession of segments, covering the efforts over a period of about eight decades, partly before and some time after the initial publication of Kraepelin's monumental work. Another segment is represented by the occupation with the problems of mental deficiency. During a long period of stagnation, interrupted only by Paracelsus' discovery of the connection between endemic goitre and intellectual stunting, the feeble-minded were regarded as a homogeneous group. The seemingly solid wall believed to be made up of identical material was dented slightly by Langdon Down's description in 1866 of what he first called Kalmuck idiocy and later came to be spoken of as mongolism. From then onwards, ever new entities were singled out and studied separately. Contributions came from various sources. We owe the knowledge of amaurotic family idiocy to the British ophthalmologist-surgeon Tay and the American neurologist Sachs; of dementia infantilis to the Austrian educator Heller; of phenylketonuria to the Norwegian veterinarian Fölling. A compact unit emerged which had its own experts, facilities, journals, and congresses. It sequestered itself from the rest of the concerns about child development and child behaviour to the extent that, at least on the North American continent, only a negligible fraction of the medical members of the American Association on Mental Deficiency have found it necessary to affiliate themselves with the American Psychiatric or Orthopsychiatric Association. Exciting things have happened within this unit, especially in the past three decades, owing to advances made in neuropathology, endocrinology, biophysics, biochemistry, psychology, and education.

As the parade of segments marches past, education is next in line. After compulsory school attendance had become an established institution, the educators became increasingly concerned about problems of learning and conduct among their pupils. Psychiatrists, for the most part, kept themselves aloof and thereby forced the teaching profession to look for its own solutions. The movement began in France and was pursued there with remarkable vigour. In Central Europe, a group, under the banner of what was termed *Heilpädagogik* (remedial education), undertook, under the leadership of Heller, Hanselmann, Isserlin, and Busemann, to make itself responsible for as much amelioration as was possible in the educational setting. Much was accomplished in this enforced isolation. The second edition of Hanselmann's *Einführung in die Heilpädagogik* (1933) showed a breadth of experience which might well arouse the envy of many a psychiatrist. The labours of these educators resulted in Europe and in America in organized practical arrangements for the special education of the intellectually, sensorily, neuro-orthopaedically, and neurotically handicapped children.

A delegation from criminology is next in the procession. In the 1890's a number of civic-spirited men and women found the then existing retaliatory attitude toward young offenders objectionable and detrimental to their development. They exerted all the political influence they could muster. As a result, South Australia in 1895, Illinois and Colorado in 1899 passed statutes establishing juvenile courts in which delinquent children were to be handled separately



and differently from adult violators of the law. Since then, juvenile courts have become an established institution. The presiding officers are mostly jurists, assisted often by a staff of social workers, paediatricians, and psychiatrists. In the case of the more severe offenders, re-education and rehabilitation, with or without the aid of psychotherapy, are channelled through special units known as reformatories, correctional or training schools. The names of William Healy, August Aichhorn, Sheldon and Eleanor Gluck are intimately connected with the study of juvenile delinquents.

The procession continues. Psychology joins the ranks. Around the turn of the century, psychologists shifted their emphasis from armchair contemplations to actual attention to real people. Alfred Binet is usually and, I believe, correctly hailed as the great innovator. No longer speculating about the attributes of an abstract soul, he let live children come unto him and, initially for the benefit of French school authorities, inaugurated an era of concrete study and the measured comparison of individuals with regard to certain areas of functioning. There came, after a few earlier examples set by Preyer in Germany, Sully in England, and Compayré in France, a spurt of stage-by-stage examinations and recordings of the gradual emergence of motor, perceptual, conceptual, linguistic, and social behaviour. Diaries, interrogations, and a variety of test batteries combined to get together a set of data which, as developmental psychology, has made invaluable contributions. Much information has come—to name but a few—from the work of the Böhlers, William Stern, David Katz, E. Claparède, Jean Piaget, and Kurt Lewin. Following this trend, Arnold Gesell and his co-workers were able to set up a normative scale of infantile development, beginning within a few weeks after birth.

The next marcher in the parade, psychoanalysis, passes by with éclat and fanfare. The awe-inspiring genius of one man created a fascinating system which has had a powerful influence on Western civilization. Freud, on the basis of anthologies of neurotic adults' more or less directly elicited reminiscences, published his theory of infantile sexuality in 1905, three years before he saw any one child professionally. He gave special heed to a set of lawfully progressing centrifugal forces centred around a broadened concept of libido and assumed to govern the development of children's personalities. Freud's profound wisdom and honesty is evident in every one of the 24 pages of the second of the Three Contributions to the Theory of Sex, entitled *Infantile Sexuality*. In this short space, there are not fewer than 55 passages in which the remarks are qualified by "probably", "perhaps", "apparently", "I believe", "it is possible", "as it were", "so to say", "may well be", "it might be supposed", "it may be assumed", "we may gain the impression", etc. This collection of probabilities, possibilities, assumptions, beliefs, opinions, conjectures, impressions and analogies, not as yet validated by dispassionate scrutiny, was somehow transformed into certainties and decreed truths and formed the foundation of an all-embracing credo enveloping all aetiology and therapy. This insistence by many, though by no means all, of Freud's followers has threatened to make of psychoanalysis an orthodox all-or-none proposition of the kind which Adolf Meyer liked to characterize as "exclusive salvationism". On the other hand, the excellent accomplishments of Anna Freud are witness to the fact that, with a less dogmatic and more flexible application, psychoanalysis can make significant contributions to the observation and treatment of children.

The column of paraders which next appears on the scene is made up by the child guidance clinics which were inaugurated in the early 1920's. The seeds for their growth were implanted toward the end of the first decade of



this century when Clifford Beers, with the encouragement of Adolf Meyer, John Dewey, Stanley Hall, and others, founded the National Committee for Mental Hygiene. Prevention of insanity and delinquency was the key word. The idea of setting up insanity and delinquency as targets to shoot at with the arrows of preventive efforts was laudable enough, to be sure. But it implied an orientation which started out with a vision of calamity, looked upon young non-conformists as wayward youths to be snatched in time from the gates of asylums and prisons, and indulged in the practice of throwing inkwells at devils painted on the wall. Actual work with children taught the workers that proper mental hygiene is not primarily an exercise in trying to prove alarmists wrong, that emotionally upset children deserve treatment of what bothers them because it bothers them *now*, and that the greatest benefit can be derived from dealing effectively with what Douglas Thom aptly referred to as "the everyday problems of the everyday child". Under Thom's leadership, the Boston Habit Clinic opened its doors in 1921. In 1922, "demonstration child guidance clinics" were established in several cities with the aid of the Commonwealth Fund. They were called so because they were meant to demonstrate their usefulness to the communities in which they were set up. By the end of the decade, there were about 500 such clinics on the North American Continent alone. In 1930, the governments of more than 50 countries sent delegates to the first International Congress of Mental Hygiene, which was held in Washington, D.C.

The greatest contribution made by these clinics to the understanding of children's behaviour was the departure from the almost universal tendency to look for explanations one-sidedly in an individual's inherent, genetically, constitutionally, and endopathologically determined, centrifugal propensities for disturbing deviations. The focus of inquiry was broadened, beyond the curiosity about that which goes on *within* a child as he reaches out into his environment, to include the external, centripetal forces which do things *to* him and thereby help to shape his feelings and resulting demeanour. Thus ensued a searching investigation of interpersonal relationships at home and in school as motivating factors. Children's behaviour began to be correlated with parents' and teachers' attitudes, which were taken into account as part of the therapeutic strategy. The newly created concept of attitude therapy made it possible to help parents and teachers to examine, discuss, and modify those of their emotional problems which were found to be detrimental to individual children. Simultaneously, through what was called relationship and release therapy, the children themselves were given an opportunity to bring their conflicts to the surface and deal with them in a manner more comfortable and serviceable than theretofore.

The child guidance clinics, aware of the psychological and sociological implications of their job, set up the so-called clinical team of psychiatrist, psychologist, and social worker. This novel and wholesome arrangement, however, was from the beginning allowed to be frozen into a rigid system which came to regard itself as a complete, self-contained unit. Much was made of this "interdisciplinary" collaboration which closed the door to all but three disciplines, and much time, meditation, and printer's ink were spent on trying to figure out and delineate the exact role of each member of what, because of the exhibited air of sacred solemnity, I have sometimes facetiously dubbed "the Holy Trinity". There being no perfection in human enterprise, the great benefit derived from making certain types of children's behaviour problems a matter of community concern had in its wake a consciously cultivated estrangement from medicine and an exclusion of all those other types of handicaps



which did not fit the clinic's self-imposed limitations. Saying this does not in any way imply a detraction of the historical importance of the work of those clinics. The insights gained from the study of parent-child, sibling-sibling, teacher-pupil, and therapist-patient relationships formed a truly indispensable addition to the sum total of information gathered by the other segments which we have met in the procession.

The parade has come to an end. Psychiatry, the study of mental deficiency, education, criminology, psychology, psychoanalysis, and child guidance have each displayed before you their particular areas of interest, inquiry, and helpfulness. Few of them had more than a nodding acquaintance with one another. I must hasten to add that in every one of those pursuits there were men whose vision went beyond the circumscribed scope of the specific segment. But it was not until 32 years ago that one man, without identifying himself with any one of the segments, managed to blend all of them into a single discipline which viewed the child as the core of psychiatric endeavour—not selectively the psychotic, feeble-minded, educationally maladjusted, delinquent, or parentally mismanaged child but every child who needed psychiatric investigation and amelioration.

Such is the nature of public acclaim that the spectacular takes precedence over calm, diligent, unobtrusively persistent labour. It is perhaps because of this that the present generation has lost sight of the merits of him who should be honoured as the first all-round, comprehensive child psychiatrist. August Homburger was commissioned in 1917 by his chief, Franz Nissl, to establish a psychiatric outpatient department at the University of Heidelberg. He began to center his interest more and more on the problems of children. It is amazing how much creative work and organizational activity he was able to pack into the 13 years between 1917 and 1930, the time of his death at the age of 57 years. He stepped out of the monastic seclusion of the psychiatric department of his university and got the community at large to participate in the concerns for mental hygiene. He worked in close collaboration with courts, schools, and social agencies. He introduced a series of university lectures on psychotherapy. Mayer-Gross, in his moving obituary, has pointed out how much courage it must have taken to do this "at a time when neither official psychiatry nor official internal medicine paid the slightest attention to the significance and effects of psychogenic factors". In 1926, Homburger published his *Lectures on the Psychopathology of Childhood*. His broad orientation could not abide by the therapeutically sterile and aetiologically one-sided categorizing of Ziehen and de Sanctis. His background had given him a mastery of neurology, which served admirably in his work with children, but at the same time made him aware of the fact that cerebral anomalies alone could not account for social, attitudinal and other factors in his young patients' experiences. He set out, with a critical eye and with remarkable fairness, to round up and present to his readers the sum and substance brought together by the various segments as well as the existing theories and hypotheses. Prophetically foreseeing his role as a pacemaker, he wrote in the preface to his book: "The psychopathology of childhood will—of this I am firmly convinced—experience much deepening and enrichment in the years to come. Whatever I may have to say in these chapters bears the nature of transitoriness and is still anchored in tradition." His modesty apparently did not allow him to admit to himself fully that, with all due respect for precedent and while putting up a warehouse of accumulated knowledge and thought, he himself was the originator of a new tradition—that of an inclusive concept of the psychopathology of childhood or child psychiatry.



It was toward the end of 1930, the year of Homburger's death, the year of the first International Congress of Mental Hygiene, the year of the White House Conference on Child Health and Protection, that Adolf Meyer, Edwards A. Park, Stewart Paton, and Ludwig Kast of the Josiah Macy, Jr., Foundation engaged me for an excursion into territory until then neglected by psychiatrists. The preliminary task assigned to me was to consist of "an investigation of the rank and file of patients in the paediatric clinics for the formulation of psychiatric problems, the mastery of which should be made accessible to the paediatrician to serve him as the psychopathological principles in dealing with children".

You have undoubtedly noticed, and possibly been puzzled by, the fact that paediatrics, contrary to logically justified expectation, was conspicuously absent from the procession which has passed before you. Lest the inference be drawn therefrom that the medical child specialists were indifferent about issues involving their patients' intellectual, emotional, and social functioning, it is well to remember that as far back as in 1889 Jacobi, one of the pioneers of American paediatrics, spoke of the desirability of making use of psychiatric knowledge in his specialty. But as no help was offered from psychiatric quarters, a few paediatricians went forth to explore the field for themselves. Rachford's *Neurotic Disorders in Childhood* (New York, 1905), Guthrie's *Functional Nervous Disorders in Childhood* (London, 1907), and Czerny's *Der Arzt als Erzieher des Kindes* (Berlin, 1908) were outstanding efforts in this direction. This essentially homegrown crop was kept from withering by a few members of the paediatric specialty. It is not generally known, for example, that the more recent detailed studies by Goldfarb, Spitz, and Bowlby of the effects of early psychological deprivation were preceded by pertinent observations on the part of two paediatricians. In 1915, Chapin, in an article entitled *Are Institutions for Infants Necessary?* advocated the boarding out of infants so that they might receive individual care and affection. In 1942, just one year before Goldfarb's first report, Bakwin's classical paper, *Loneliness in Infants*, painted a "fairly well defined" clinical picture of the hospitalized infant whose personal needs are neglected aside from the exclusive attention to his somatic illness. Nor should one overlook the fact that in 1919, before the advent of the child guidance clinics, Hector Charles Cameron, physician in charge of the children's department of Guy's Hospital, gave evidence of much sympathetic understanding of emotional features and parent-child relationship in a charming, often reprinted book, *The Nervous Child*, and later in a chapter contained in the 1929 edition of Garrod, Batten and Thursfield's textbook of paediatrics.

But these insights were sporadic and not at all the common property of the paediatric profession, even though its practitioners, often prodded by the demands of sophisticated parents, became increasingly eager to receive assistance from psychiatry. What did they find? The child guidance clinics, as they came along, ignored them completely; the "team" gave them the cold shoulder. Perusal of the literature resulted in bewilderment. Veeder, shortly before he became editor of the *Journal of Pediatrics*, had this to say at the White House Conference in 1930: "I have a very definite feeling that the psychiatrist and psychologist have contributed somewhat to the paediatric attitude of suspicion, or scepticism. The psychiatrist above all other people with whom I come into close contact has a penchant for obfuscating his thought with a most perplexing, and I feel unnecessarily complicated verbiage."

Such was the situation when in November, 1930, I set foot at the Harriet Lane Home, the children's division of the Johns Hopkins University School of



Medicine, as the first pseudopodium stretching out into paediatrics from the psychiatric amoeba. A cautious attempt by von Pirquet in 1911 to have a psychiatric observation station, headed by E. Lazar, at the University Children's Hospital in Vienna was not even locally too successful because at that time child psychiatry and paediatric concern with it were both still in the stage of embryonic incipency.

Very soon after the assumption of my duties, an anonymous donor, to whom I shall be forever grateful, left on my desk the reprint of an article, just off the press, entitled *The Menace of Psychiatry*. Its author was Joseph Brennemann, an eminent paediatrician known for his long experience and sound judgment, a man whose word had a great resonance among his colleagues. Brennemann declared unequivocally: "There is not only a menace of psychiatry, but it is already seriously in our midst." He castigated the blatant overpopularization and oversentimentalization of child psychology, the overevaluation of certain standardized tests, and the conflicting claims of some of the speculative, aggressively vociferous, and overbearingly dogmatic "schools". Thus Brennemann's blast presented a healthy challenge, the call for a sweeping house-cleaning which deserved to be at least as welcome to psychiatrists as to the paediatric group which he addressed. For here was sound criticism of features which were not so much a menace of psychiatry as they were a menace to psychiatry.

Brennemann's warning enhanced my already firm resolution to avoid these and many other pitfalls. Coming from a pluricultural and plurilingual background, having emancipated myself from the theological and political absolutism fed me in my youth, falling easily into step with Meyer's practised advocacy of a scientifically objective, self-scrutinizing, pluralistic and relativistic attitude, I found it impossible to limit myself to any of the segments which have passed before you in the procession. Besides, the setting itself made any such restricted alignment impractical. The children who came to the wards and outpatient department just did not sort themselves in accordance with anybody's preoccupations. They were brought in because they were feverish, coughed, had rashes, lost weight, had fractured a bone, were jaundiced, convulsed, held their breath, stuttered, wet the bed, stole, did poorly in their studies. They came with these and many other complaints. Here, then, was an unprecedented opportunity, offered in no other setting, to study children and their manifold problems in an environment from which no patient was ever kept away for any reason and in which the watchfully and hopefully waiting paediatricians were trying to assess the services rendered by psychiatry and its invited representative. For paediatricians are, as all medical men and all other scientists everywhere should well be, governed by the desire for factual demonstrations, for the careful perception of reality which hesitates to accept even the most beautifully constructed hypotheses unquestionably at their face value.

This psychiatric-paediatric alliance in the daily work with individual children made it possible to utilize all the previously recorded observations and discoveries and to introduce the sum total as the discipline of child psychiatry as a medical concern with psychological, educational, social and cultural ramifications; as a legitimate science within the framework of medical practice, teaching, and research; as a child-centred enterprise engaged in the diagnosis, treatment, and prevention of developmental and behavioural deviations with and without organic involvements. That this trend toward synthesis has more recently spread over the entire field of psychiatry, has been made



clear by the publication in 1957 of a volume edited skilfully by H. D. Kruse and entitled *Integrating the Approaches to Mental Disease*. Starting with the deplored awareness of what was referred to as insular grouping, fragmentation, segmentation, and provincialism, an attempt was made by 48 men, including your Hargreaves, Rees, Richter, and Slater, to get together on fundamentals and outline areas of acceptance by all and of non-acceptance by some. It is rather pleasing to know that child psychiatry, under the influence of Adolf Meyer, has gone a long way in striving for this aim over a period of nearly thirty years.

This is not to say that, even though the ranks have been closing, there is complete uniformity of opinion and method. As a matter of fact, I am not sure that such uniformity is a condition to be coveted before that day in the distant future when all the aetiological, diagnostic, remedial, and prophylactic facts will lie palpably in the palms of our hands. On the contrary, some of us have found it necessary to speak out against a recurrent tendency to impose an inflexible system of thought and action on all patients, regardless of the nature of their difficulties. This tendency seems to have persisted, in one form or another, since the time of Maudsley who, asserting that "whosoever distinguishes well teaches well", felt called upon to militate against uniform procedure. He wrote that for adequate strategy "it would be necessary to have a full and exact knowledge of the construction of the individual mind as well as of the proper remedy: to know the particular character, the special fault of it, the kind of disorder to which the fault was prone to lead, and the exact conditions of life which would be the fit remedy; for different pursuits might wisely be used as so many remedies for different defects of character."

These words, written in 1895, have a peculiarly familiar ring if one considers the still existing controversies about the need for diagnostic accuracy and for investigative as well as therapeutic methodology. The issue, highlighted so well by Maudsley half a century ago and still alive in our midst, is essentially this:

There are those whose medical training has kept in the foreground of their responsibility the obligation to view each patient as—if I may use Meyer's term—a unique experiment of nature. It is the physician's duty to devise and refine means of investigation that would help him to become cognizant of this uniqueness as an indispensable preparation for the regime best adapted to the requirements of the individual. In so doing, whether he be an ophthalmologist, a cardiologist, an orthopaedist, or an adult or child psychiatrist, he notices that there are certain combinations of features which, though never completely identical, are similar enough to justify the recognition of specific diagnostic categories. This, after all, has been Kraepelin's great accomplishment, that he perceived, described, and studied these similarities and thus brought order into the hitherto unorganized welter of mental diseases. This search for diagnostic clarity is still going on in the wide area of child psychiatry, with the added awareness that, within each sufficiently defined category, the imperative consideration of genetic, physical, intellectual, situational, and experiential differences presents a fascinating invitation to deal with each child as an exceptional, unduplicated specimen.

This, however, is not a universally established tradition among child psychiatrists. There are those who, rightly dissatisfied with what sometimes, I believe erroneously, has been identified as the only concern of medicine, are inclined to turn their backs to organ pathology, description, and classification. Intrigued, as everybody should be, by the relatively new emphasis on psycho-



dynamics, there has been a tendency to elevate intrapsychic and interpersonal factors to the rank of sole determinants of behaviour, or at least as the sole determinants worthy of psychiatric attention. Certain theories have been put forth and certain methods of inquiry and treatment have been laid down which are transmitted from teacher to learner as ultimate, catechistic truths. In the process, theory and method have gained ascendancy over the patient, to whom they are applied with little curiosity about his microcosmic uniqueness. If the standard concepts and rules are not suited to his specific problem, then they are either tried out on him for a time anyway or he is sent home unaided. Under these circumstances, with medicine pushed aside, it is not surprising that the door has been opened wide to lay people, with or without a preliminary medical diploma, who have qualified as adept repeaters of the catechism.

A concrete example may serve as an illustration of the manner in which the two groups have approached the problem of diagnosis. During the past two decades, there has been a revival of interest in the infantile psychoses. There has been, especially in the United States, an unprecedented wealth of publications on childhood schizophrenia. In them, two more or less antithetical trends are clearly discernible: one which tries to single out specific, circumscribed, carefully defined syndromes on the basis of precise semeiology, and one which tends to dilute the concept of schizophrenia, with not too much regard for the intricacies of differentiation not only between those syndromes themselves but also between them and conditions of innate mental deficiency. It is true, of course, that, as instances of spontaneous or therapeutically induced improvement have demonstrated, average or better than average original endowment can be dammed up by the psychotic process. It is also true that, as Weygandt pointed out in his monograph written for Aschaffenburg's *Handbuch* in 1915, idiotic and imbecile children can present oddities of behaviour reminiscent of schizophrenic phenomena. There is no denying that overlapping symptomatology creates problems in trying to distinguish between different illnesses which have a number of features in common. But the problem is definitely not solved by the decree that the sharing of symptoms makes the conditions identical or that because of the partial resemblance a differentiation is unnecessary.

Nevertheless, on the assumption that lack of adequate mother-child relationship underlies *all* arrest or fragmentation of personality structure at different stages of development, Beata Rank advocated the sweeping notion of the "atypical child". She declared that, in using this term, she referred to "more severe disturbances in early development which have been variously described as Heller's disease, childhood psychosis, childhood schizophrenia, autism, or mental deficiency". Similarly, Szurek, announcing the consensus of his co-workers at the Langley-Porter Clinic in San Francisco, made this statement: "We are beginning to consider it clinically (that is, prognostically) fruitless, or even unnecessary, to draw any sharp dividing lines between a condition that one could call psychoneurotic and another that one could call psychosis, autism, atypical development, or schizophrenia." This is a return to pre-Kraepelinian looseness which throws all the laboriously assembled and refined diagnostic criteria to the winds as irrelevant impediments on the road to treatment. Treatment, under these circumstances, has become a more or less stereotyped method applied to all comers and dispensed as hours of psychotherapy. The therapeutic cart is put before the diagnostic horse and it seems that sometimes the horse is left out altogether.



It is perhaps not out of place if, at this juncture, I beg of you to let me dwell briefly on the role of psychotherapy in child psychiatry. Let me begin with an expression of unreserved admiration for the methods which have been introduced in order to help children to reveal their feelings to themselves and to the therapist. Play, drawing, clay modelling, thematic apperception tests, and other projective tools have proved of inestimable value. Having said this, I wish to add that psychotherapy, no matter how essential it is in the overall remedial strategy, is but a part of the therapist's responsibility. While it aims at an adjustment from within outward, there is ample room for help extended from without inward. I think you will agree with me that, while our professional literature abounds in detailed accounts of excellent observations and more or less realistic interpretations of happenings during therapeutic interviews, the intrinsic goal of psychiatric treatment has never been defined clearly and unequivocally. Is it the purpose to learn and teach specific methods or, as some say, techniques to be employed indiscriminately in every instance, unmindful of the uniqueness of the problems which confront us? I shall never forget the young man just out of training who on a visit to our clinic was stunned by the absence of a sand box and running water in the treatment rooms; it was incomprehensible to him how there could be any child psychiatry without those two implements which, so he had been taught, were absolutely essential parts of the arrangement. Does not this smack too much of an attitude which fosters the rearing of a generation of therapeutic mechanics?

If I may venture a concise statement about the goal of psychiatric treatment, it is this: The sum total of efforts expended in order to help a patient to attain *his* optimal condition of comfort and smoothness of functioning. Such a formulation recognizes that, with the great variety of conditions encountered in the wide realm of child psychiatry, the attainable optimum differs with each individual's somatic, intellectual, and socio-cultural propensities, all of which must therefore be investigated carefully before a plan for treatment is outlined. The plan may, depending on the findings, involve parent counselling, psychotherapy with the child, the correction of impaired vision, adequate classroom placement, the supply of sufficient food and clothes, and any other arrangements in keeping with the patient's specific needs. Patient-centred, individualized programmes with concrete aims differ essentially from less goal-defined, method-centred journeys into the unknown with the diffuse hope that somehow this will eventually produce a state of blissful "normalcy" in the image of the therapist's conception of suburbanite propriety.

The children who come streaming to a large paediatric clinic and to its psychiatric station recruit themselves from mansions, middle-class homes, tenement houses, and shacks, from psychometrically intelligent and unintelligent families, from backgrounds of affectionate acceptance, agitated over-protection, perfectionistic disapproval, or overt hostility and neglect. They arrive with healthy bodies, minor physical ailments, and more severe congenital or acquired anomalies and diseases. They are brought with no complaints about their behaviour, with everyday problems from which I for sure was not, and possibly some of you were not, totally exempt, with varying degrees of developmentally determined intellectual shortcomings, with anxiety-laden neuroses, and occasionally with major psychotic disturbances. Not one of them deserves to be pushed aside or sent off because he does not fit the preordained requirements of a selectively dosed therapeutic procedure. No physician would, or should, be content with an attitude which makes the choice of patients depend



on the method instead of making the choice of methods depend on the needs of the individual patient.

I realize that some of the trends of which I have spoken pertain to psychiatric work with adults as well as with children. I also realize that child psychiatry, being a newcomer among the medical sciences, still experiences enough uncertainty to warrant a great deal of experimentation. I grant that some of the restricted preoccupations with psychodynamic factors can be understood as an overreaction to the earlier disregard of these factors and to earlier satisfaction with the mere description of symptoms and with mere diagnostic labelling with little or no heed to the foundation and meaning of the patient's emotional involvement. But I believe that the time has come when all of us in the field should be willing to submit theories and methods to a sober evaluation of results. It is time for a bit of reality testing. It is time to examine the existing free-floating generalizations in relation to available data of observation and at the same time to build further generalizations on the basis of such data. With this in mind, I can find no more suitable quotation with which to conclude my address than the reiteration of a plea by Henry Maudsley, who said: "Observation should begin with simple instances, ascent being made from them step by step through appropriate generalizations, and no particulars should be neglected."



# THE ORIGIN AND SPREAD OF DEMENTIA PARALYTICA

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## PART I

DEMENTIA paralytica<sup>1</sup> is a declining disease. Deaths due to it in England and Wales were first recorded by the Registrar General in 1901 and since that year, when the number was 2,272, the annual figure has fallen steadily until in 1957 it was only 68. Moreover, there is evidence (adduced below) that not more than a small part of this decline can be attributed to improvements in medical treatment. The fear that there might be a recrudescence of dementia paralytica as a result of the spread of syphilis during the second world war has not so far been realized and it seems likely that what is now, in Great Britain at all events, an obsolescent disease will soon become a rarity. Yet there are many unsolved problems in its history. We do not know, for example, why the alleged references to this striking disease were so few and so inadequate until the third decade of the nineteenth century. We do not know why its recognition in many countries was so tardy in spite of the clear description given by the French alienists. Nor do we know why the disease, which at the start of the nineteenth century seems to have been predominantly one of males, has gradually—and at different rates in different countries—become much more evenly distributed between the sexes.

The principal aim of the present essay is to recall some aspects of the history of dementia paralytica. It is a history of which psychiatrists may very properly be proud but which, perhaps, is less well known in general medicine than it deserves.<sup>2</sup> A modern Oxford historian has observed that, as all history

<sup>1</sup> The disease which all English-speaking physicians recognize by the term "general paralysis of the insane" or "G.P.I." has suffered from a plurality of names. Calmeil, in 1826, called it "paralysie générale des aliénés", which was no doubt an improvement on Bayle's "arachnitis chronique" of 1822, in that it did not assume an unproved pathological cause. But later, when Baillarger and others believed they had discovered cases of general paralysis without insanity, a new name seemed necessary, and Falret in 1853 advocated "folie paralytique". However, Calmeil's term was by that time fairly entrenched and remained the favourite in spite of Salomon's quip (1862) that "he who is generally paralysed is certainly dead". Salomon suggested the alternative "general paresis"—a term which has enjoyed a considerable vogue in America. Mickle, in his authoritative English textbook on the subject (1880), gave a list of eight English and nineteen French synonyms, but his book is still entitled *General Paralysis of the Insane*. Krafft-Ebing and other German writers favoured the name "dementia paralytica"; and in adopting this name, which I believe to be the most satisfactory one, I have had in mind not only that it over-rides the barriers of national language but also that (a) Salomon's criticism of the term "general paralysis" is unanswered, (b) the word "insane" is a legal rather than a medical term and has since 1930 been largely expunged from English statutes, and (c) the criticism that the initial letters of dementia paralytica may be confused with those of dementia praecox is no longer a valid one. Yet during the period with which this essay is mostly concerned (that is, broadly, the nineteenth century), "general paralysis of the insane" or more simply "general paralysis" was the common English usage.

<sup>2</sup> It has been strangely neglected by the historians of medicine. Neither the early history of the disease nor the name of Antoine Bayle (who is universally credited with the principal part in its delineation) are so much as mentioned in the histories of Garrison (1929), Guthrie (1945), Castiglioni (1947) or Major (1954); and there is only a passing reference in Mettler (1947). Henry, in his *History of Medical Psychology* (Zilboorg and Henry, 1941) gives a good account, but the story should have a place in the general history of medicine.

must be a selection from the facts, its presentation is often made more pointed by ordering the facts to illustrate some general theory or interpretation of the events. In the hope of adding new interest to an old tale, I have adopted this method and shall bring forward evidence to suggest: first, that dementia paralytica, from being a rare disease or even non-existent, suddenly assumed epidemic prevalence in northern France soon after the Napoleonic wars; second, that from France the new disease spread slowly across Europe and to the New World, gradually changing in its clinical manifestations; and third, that over and above the effects of treatment and prevention there has been a natural decline in its prevalence during the past fifty years. As far as they can be upheld, these points will support the well-known hypothesis that dementia paralytica is due to a special "neurotropic" strain of the syphilitic virus, for they will allow us to put forward the view that a mutation giving rise to the neurotropic strain occurred in northern Europe towards the end of the eighteenth century; that the spread of this mutant strain explains to some extent the curious time lapse before the disease was recognized in other countries; and that, comparably with the great epidemic of syphilis in the late fifteenth century, the new disease slowly changed in its prevalence and clinical manifestations.<sup>1</sup> It must be admitted that the neurotropic hypothesis has never had a great appeal for the best authorities on the subject. Nevertheless, it has not been discredited and still provides a possible explanation of some of the historical facts about dementia paralytica which are otherwise very difficult to explain.

The clinical and pathological characteristics of dementia paralytica were first clearly delineated during the third decade of the nineteenth century by physicians working in the mental hospitals of Paris. These men took the view that the disease which they described had always been in existence and that it had simply escaped the notice of earlier workers. Thus, in his *Maladies du Cerveau* (1826, Introduction, p. xxiii), Bayle<sup>2</sup> says that chronic meningitis, which was very common in the insane and which he first described in 1822, "had never been noticed before". Georget (1820, p. 130) simply states that among demented patients "the commonest disorder of muscular power is weakness, general or partial, of voluntary movement" and makes no suggestion that there has been a recent increase in prevalence of this disorder. Calmeil (1826, p. 7) says: "The species of paralysis that I wish to describe under the title of general paralysis of the insane is far from rare; however, as far as I know, its natural history has not yet been traced in detail." By the time Esquirol wrote his *Des Maladies Mentales*, dementia paralytica had become a well-recognized condition; yet he refers (1838, vol. 2, p. 263) to the writings of Calmeil and Bayle as only confirming "the sad truth to which I drew attention in 1805" (which was, the incurability of insanity complicated by paralysis), and this observation does not suggest that Esquirol thought there was anything

<sup>1</sup> The view that the fifteenth century outbreak of syphilis was due to a mutant strain of the spirochaete has been succinctly put in the *Lancet* (1957). See also Hirsch (1885), Mott (1908), Morris (1912), Sudhoff (1926), Whitwell (1940), Lees (1950). Some of the arguments for and against the neurotropic hypothesis of dementia paralytica are summarized by Hutton (1941) and Wilson (1941, Vol. I, Ch. 17). Curiously, however, neither of these writers makes reference to the suggestive (though limited) epidemiological evidence mentioned in support of the hypothesis by Stewart (1924). The present essay is, in one sense, an attempt to add to this epidemiological evidence.

<sup>2</sup> The life, character and works of Bayle and of other eminent French psychiatrists have been described by René Semelaigne (1894, 1930). The relevant parts of Bayle's inaugural thesis of 1822 on which rests his claim to have given the first clear description of dementia paralytica have been translated into English by Moore and Solomon (1934).



new in the occurrence of paralysis in the insane. This belief in the antiquity of dementia paralytica persisted through much of the nineteenth century. Writing what he claimed to be the first separate volume on the subject by a British author, Thomas Austin states (1859, p. 1), "General paralysis, though it had doubtless existed from the earliest period of insanity, eluded observation or at least never so fixed the attention of those who must have witnessed it, as not to be recognized and described as a distinct disease till the early part of the present century." Sankey, that sound and erudite lecturer on mental diseases to University College, London, says (1866, p. 178), "It is quite a settled point that the disease was not recognized till a comparatively recent date but distinct allusions to the symptoms may be found in authors of very ancient times"; and he later gives his opinion that the "apparent novelty" of the disease is largely due to slowness in its recognition. Writing the chapter on Progressive General Paralysis in Charcot's *Traité de Médecine*, Ballet and Blocq (1894) observed that—"The discovery of general paralysis as a distinct disease with its own characteristic lesions . . . dates from 1822 . . . Before this, general paralytics had been observed and certain peculiarities of their illness noted, but no one had thought to isolate it as a morbid entity distinct from other nosographic species recognized at the time."

Yet there is strong evidence, marshalled by Kraepelin (1913, p. 163; 1927, p. 1135), that dementia paralytica must in fact have been rare before the Parisian outbreak. We may therefore consider why the earlier writers should have taken the view that it had always been prevalent, a view not uncommonly accepted even today. Two reasons may be brought forward. In the first place, it was generally believed during the eighteenth century that diseases, like plant and animal species, were fixed and immutable. The works of Linnaeus had encouraged naturalists to study with increased attention the attributes of living organisms so that each could be classified into its particular species, order and genus. This stimulus soon spread to medicine and the study of *nosography*, the classification of diseases into distinct and related types, became a popular and respected specialty.<sup>1</sup> But in the days before Darwin and Wallace it would not have occurred to the physician that a disease (especially a chronic disease) might arise *de novo* any more than the naturalist would have expected to find a newly created species. In the second place, the syphilitic origin of dementia paralytica was unsuspected or unproved during the nineteenth century; the principal causal factors were thought to be alcoholic and sexual excess, and those who upheld this view could scarcely have believed that the disease was a new one in history.<sup>2</sup>

<sup>1</sup> What Linnaeus had done for botany and Cuvier for zoology, Cullen of Edinburgh (1769) attempted for general medicine and his pupil, Thomas Arnold, for insanity. Arnold's *Observations on Insanity* (1786) does not appear to have exercised much influence on his contemporaries and remains a curious relic of the attempts to classify on philosophical grounds "those disorders of the *mind* which still resist the discriminatory powers of our scientific age". Philippe Pinel, a friend of Cuvier, also published a classification of mental diseases, but though his *Nosographie philosophique* (1798) proved in the end as sterile as Arnold's *Observations*, these works may serve to indicate one significant point: that during the latter part of the eighteenth century, mental disorders were carefully studied with a view to the classification of syndromes and we may pardonably be astonished that so striking a disease as dementia paralytica, if it had been anywhere near as prevalent as it later became, could have escaped notice.

<sup>2</sup> Maudsley was the weightiest proponent of the theory of sexual excess. In the first edition of his *Physiology and Pathology of Mind* (1867, p. 360) he takes the very moderate view that the commonest cause of dementia paralytica is intemperance, alcoholic or sexual, and, acknowledging that these are nevertheless not infrequently absent, adds that then "some sort of hereditary taint is likely enough to be present". In 1873 his views are more definite and his contribution to an aetiological discussion is reported in the *Journal of Mental Science* (1873)

The nineteenth century belief that dementia paralytica had always existed led to search for descriptions of its symptoms and signs in the writings of earlier physicians. A consequence of this search is the frequency with which Thomas Willis is quoted as having given the first description in 1672. The evidence for his claim is worth re-examining. I have been unable to discover who first drew attention to the relevant passages in the *De Anima Brutorum*, but Sankey (1864) refers to them and thereafter most writers, especially English ones, quote them as a matter of course.<sup>1</sup> The passages are as follows:

"I have observed in many that when, the Brain being indisposed, they have been distempered with a dullness of mind and forgetfulness, and afterwards with a stupidity and foolishness, after that have fallen into a Palsie, which I oft did predict; to wit, the Morbific matter being by degrees fallen down, and at length being heaped up somewhere within the Medullar Trunk (where the Marrowy Tracts are more strained than in the Streaked Body) to a stopping fulness. For according as the places obstructed are more or less large, so either a universal Palsie, or an half Palsie of one side, or else some partial resolutions of members happen . . .

"The oppilative or stopping Particles being fallen down from the Brain and carried forward into the oblong Marrow, enter into the Nerves destined to the Muscles of some parts of the Face, and by obstructing the ways of the Spirits in them, bring forth the Palsie in the Tongue, and sometimes a loosening of these or those Muscles of the Eyes, Eye-lids, Lips and other parts."<sup>2</sup>

It is, in truth, hard to see why this extract should have come to take so prominent a place in accounts of the history of dementia paralytica. A "half palsie of one side" or palsy of the tongue and eyes are not at all characteristic of the disease; Griesinger (1861, p. 396) for example says, "It is only in exceptional cases that we observe greater weakness in one half of the body, an inclination of the tongue to one side, obliquity of countenance . . . Strabismus and disorders of movement of the eyes generally scarcely ever occur." Much of the description would fit the case of arteriosclerotic dementia with its slowly progressive amnesia punctuated by cerebro-vascular attacks associated with paralysis. Certainly, of the illustrative case histories which Willis gives later (pp. 174-6), most show either intra-cerebral haemorrhage at post-mortem or a satisfactory response to treatment. A scrutiny of the rest

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thus: "He would by no means venture to say that sexual excess was the sole or entire cause of general paralysis . . . but of the efficiency of sexual excesses as an exciting cause he entertained no doubt"; the excesses he had in mind were not sudden outbursts of sexual activity but "that quiet steady continuance of excesses over months or years, by married people, which was apt to be thought no vice or no harm at all." By 1879 (*Pathology of Mind*, 1st edition, p. 432) his opinion on the most frequent exciting cause is—"Sexual excess I hold confidently to have that evil pre-eminence"; and in 1895 (2nd edition, p. 465): "Were it right to ascribe it to any single cause, I should fix on sexual excess and still hold the opinion despite the dissent of those inquirers who find no evidence of such excess." Although, from our later knowledge, these extracts might tempt us to reflect on the puritan strain in Maudsley and on the Victorian attitude to sex, yet, until the weight of evidence associating dementia paralytica with syphilis became overwhelming, the theory of sexual excess explained the facts as well as any other theory and better than most. At times, however, the attempt to reconcile fact and theory strains even Maudsley's ingenuity: commenting on the rarity of general paralysis in the highlands of Scotland, "where there is of course no deficiency of women or whisky", he asserts that an open-air life and "a great deal of bodily exercise" make people less likely to be provoked into excesses and more capable of withstanding them.

<sup>1</sup> Mickle (1880, p. 2) assigns the chief merit of the discovery of general paralysis to "Willis, Haslam, Bayle and Calmeil, especially the first three". I doubt whether any Frenchman would agree.

<sup>2</sup> Most writers quote in the original Latin, but for the benefit of those whose Latin is as rusty as my own, I give the translation made by Samuel Pordage in 1684. The "streaked body" is, of course, the corpus striatum. Willis's explanation of paralysis is based on the theory that normal functioning of the nervous system depends on the unimpeded flow of vital spirits from the brain down through supposed channels in the nerve tracts. A "morbific" process manifested itself by the generation of "stopping" particles (or "oppilative" particles, from the Latin, *oppilare*, to stop up) in the brain, and these, carried down into the narrower nerve channels, tended to clog them and so impede or prevent the flow of vital spirits.



of the chapter shows that Willis's concept of "palsie" was a wide one and included simple exhaustion and weakness. "Long and immoderate sadness, a Consumption, a Scorbutic Atrophy or wasting, being long fixed in Bed, unhealthy old Age . . . at length brings on a *Palsie*" (p. 165). Again, on a different aspect, he says (p. 166), "They who are frequently and grievously obnoxious to the Colick at length become also paralytic. The cause is so frequent here, that the succession of this Disease is accounted among its *prognosticks*." This passage may suggest lead poisoning,<sup>1</sup> but certainly not dementia paralytica. In the case of the "young and handsome woman" who, after suffering "a most cruel and continual Colick"; became "molested with a stupefaction", Willis observes again that such distempers often forerun a "palsie", which indeed followed here so that "not only all her greater Members, as her arms and legs, but almost every lesser joynt or limb was almost wholly loosened that she could not move hand nor foot or the fingers or toes of either". Yet after a month or two the young lady recovered completely. From such examples we may reasonably conclude that Willis, in observing that states of "stupidity" were sometimes followed by "palsie", had in mind diseases altogether different from dementia paralytica. Moreover, if brief generalizations are going to be adduced as evidence for the existence of dementia paralytica, why pick on Willis? Other passages from much earlier writers might equally well be adduced. Thus Hippocrates (quoted by Whitwell, 1940) says, "Mental weakness associated with a shaking voice, a tongue and voice tremulous, indicates a grave form of mental disorder",<sup>2</sup> and Whitwell quotes similar passages from Celsus, Aretaeus, Galen and Avicenna; one from Boerhaave in 1761 seems closer to the mark than Willis's: "if in an apparently healthy young man noticeable tremor occurs about the lips or eyelids with stammer, then paralysis will follow and death from apoplexy." Such passages have been ignored (rightly enough), yet the references to Willis continue. Morton's *Medical Bibliography* (1954), for example, states simply that Willis's *De Anima Brutorum* "includes a description of general paralysis, probably the first definite recognition of the condition"; Garrison (1929, pp. 263 and 827) makes a similar assertion. These continued claims on Willis's behalf are the more surprising as they are contrary to the authoritative opinion of Robertson (1923); Robertson thought it "much more likely that Willis refers to senile or arteriosclerotic dementia". The fact is that no claim for the recognition of a disease can safely be based on a brief generalization; it must rest on detailed case-histories of which one *may* be sufficient but more than one is always preferable. Willis indeed gives us case-histories, but these serve only to weaken still further the claim that he described dementia paralytica.<sup>3</sup>

<sup>1</sup> Griesinger (1861, p. 172) wrote: "In lead poisoning the excitement passes frequently into stupor; besides, there are often cramps and paralysis: the prior existence of lead colic . . . may assist in forming the diagnosis". Meryon (1864), discussing a case of plumbism, says: "for nearly two years the characteristic colic of lead-poisoning preceded the paralysis; and such is the invariable course of the disease." In the seventeenth and eighteenth centuries, not only was industrial plumbism common but "outbreaks of lead poisoning occurred throughout Western Europe as the result of the addition of lead to wine to promote fermentation and because of its employment in the manufacture and storage of cider and in materials for cooking vessels and other household articles" (Cantarow and Trumper, 1944).

<sup>2</sup> Bucknill and Tuke (1858, p. 17) also refer to this passage from the *Corpus Hippocraticum*: "We might recognize here" (they say) "the symptoms of incipient general paralysis."

<sup>3</sup> That a single case may be sufficient is illustrated by another of Willis's case histories in the same chapter "On Palsie" of the *De Anima* (p. 167). The "prudent and honest Woman" with the "spurious Palsie" who, when she spoke too long or too eagerly, became as mute as a fish for an hour or two, must surely, as Guthrie (1903) pointed out, have suffered from myasthenia gravis.

A much more likely contender for the first English account of the disease is John Haslam, apothecary to Bethlem Hospital. In 1798 the first edition of Haslam's *Observations on Insanity* was published, and his Case 15 (p. 115) is usually upheld as the most convincing pre-Parisian description of dementia paralytica. Robertson (1923) says it "presents a clinical and pathological picture so typical that no one has ever doubted the diagnosis". Now we are told that the patient, a man of 42, admitted to Bethlem Hospital in 1795, "had some years before travelled with a gentleman over a great part of Europe" and therefore, if the case was one of dementia paralytica, we can imagine that he might have acquired the disease from the same source as, on our hypothesis, led to the Paris outbreak. On the other hand, we are dealing with an isolated case and authorities are in agreement (see, for example, Krafft-Ebing, 1894, pp. 75 and 78; Kinnier Wilson, 1954, Vol. 1, p. 553) that in any single instance the differential diagnosis on clinical and gross anatomical grounds between dementia paralytica and cerebral syphilis may be impossible; indeed, the facts that in Haslam's case the first sign of illness was a sudden headache and that the mouth was "drawn aside" are perhaps more suggestive of the latter condition. Moreover Leigh (1955) has commented on the post-mortem aspects of this case that "it is impossible to hold that he (Haslam) has given a recognizable description of the macroscopic anatomy of general paresis". A more serious objection to the establishment of our hypothesis is the much-quoted observation of Haslam on paralytic affections of the insane. The passage below is taken from the first edition (1798, p. 120) of the *Observations on Insanity*, the sentences in brackets being those added in the second edition (1809, p. 259).

"Paralytic affections are a much more frequent cause of insanity than has been commonly supposed (and they are also a very common effect of madness; more maniacs die of hemiplegia and apoplexy than from any other cause). In those afflicted from this cause we are, on inquiry, enabled to trace a sudden affection, or fit, to have preceded the disease. These patients usually bear marks of such affection, independently of their insanity: the speech is impeded and the mouth drawn aside; an arm or leg is more or less deprived of its capacity of being moved by the will; and in by far the greatest number of these cases the memory is particularly affected. (Persons thus disordered are in general not at all sensible of being so affected. When so feeble that they can scarcely stand they commonly say they feel perfectly strong and capable of great exertions. However pitiable these objects may be to the feeling spectator, yet it is fortunate for the condition of the sufferer that his pride and pretensions are exalted in proportion to the degradation of the calamity which affects him.) Very few of these cases have received any benefit in the hospital; and from enquiries I have been able to make at the private houses where they have been afterwards confined, it has appeared that they either died suddenly from apoplexy or have had repeated fits from the effects of which they have sunk into a stupid state and have gradually dwindled away."

This passage is usually taken to indicate that dementia paralytica must have been common at Bethlem Hospital as early as 1798; but I shall attempt to dispute that view.

First, Haslam's description differs in many respects from the classical descriptions of dementia paralytica. In dementia paralytica, the mental changes are usually observed before, not after, the onset of paralysis; the paralysis develops gradually, not suddenly; it is rare for a single limb or the ipsilateral limbs only to be involved; and while apoplectiform fits are common, persistent hemiplegia is rare and death in apoplexy is also rare. As the clinical signs of dementia paralytica have changed somewhat during the past century, I will support my assertions by quoting from early, but authoritative, writers. As regards the relation between the time of onset of the mental and of the paralytic



symptoms, Calmeil (1826, p. 336) says that "at Charenton, paralysis almost always appears after the onset of the mental disturbance", and Prichard (1835, p. 106) says: "It results, from a great number of observations purposely made by MM. Calmeil, Esquirol and others, that general paralysis commences sometimes long after mental derangement; in other instances simultaneously with it; while in comparatively a few cases it precedes the manifestation of disorders in the mind." As regards the mode of onset of the paralysis, the disease runs its course "gradually and even slowly, the symptoms appearing and developing themselves in a regular succession" (*ibid.*, p. 105). As regards the mouth, Calmeil (1826, p. 10) says that the mouth and face preserve their natural position, and Westphal (1868), who gives a very careful and thorough account of the motor symptoms of dementia paralytica, says, "Unilateral paralyzes of the tongue or of the face either do not occur at all, or, where they have been observed, play but an unimportant part in so far as they exhibit as a rule merely transitory, suggestive and incomplete phenomena." Westphal also observes that the apoplectiform and epileptiform attacks of dementia paralytica frequently result in unilateral or bilateral paralyzes but "all these paralyzes have the peculiarity that they very soon, in the course of a few hours or days, either entirely or almost entirely disappear . . . In exceptional cases they remain persistent." As regards hemiplegia and apoplexy as a cause of death, Skae (1860) examined 78 patients dying of dementia paralytica but could attribute only one death to apoplexy and one other to exhaustion from a succession of epileptic fits; Calmeil (1826, p. 79) had earlier said that death seldom follows as the simple consequence of cerebral disease.

Second, Haslam's remarks could equally well be taken to apply to other diseases, notably chronic alcoholism. "Of all forms of chronic insanity", Griesinger (1861, p. 570) wrote, "drunkenness especially appears to possess much in common with general paralysis"; and indeed the similarity gave rise to the name "alcoholic pseudo-paresis". We know, too, that chronic alcoholism had become very common in England towards the end of the eighteenth century from the recently developed habit of dram-drinking, and its mental effects were far more common than in France, where wines rather than spirits were the national beverage. Thus Prichard (1835, p. 204) says, "Drunkenness is a much more prevailing vice in England and in Germany than in France, Italy and Spain . . . In public lunatic asylums in England, it is generally known that, in a great proportion of cases, dram-drinking is the exciting cause." In 1844, this proportion was given as 18 per cent. by the Lunacy Commissioners (Bucknill and Tuke, 1858, p. 44), though at Bethlem Hospital Sir Alexander Morison found it only 12 per cent. However, to quote Griesinger again (1861, p. 171), "it is generally recognized that in later times the abuse of spirits in England has very much diminished". We may conclude that insanity due to alcoholism must have been very common in England in Haslam's time; moreover, the increase in prevalence had only recently occurred, so that the cause of the associated dementia and paralyzes might often have been missed.

Third, the case records of Bethlem Hospital have been preserved (though somewhat incompletely) since the year 1816 and provide original and impartial evidence on the frequency with which paralysis was diagnosed by Haslam's immediate successors. I have examined these records for the three years 1816 to 1818 and find that, of 295 cases admitted during those years, paralysis or a "suspicion of paralysis" is mentioned in 19 (16 male, 3 female). However, the word "paralysis" is clearly used in the same loose sense in which Willis used it.

Any weak, stuporous or troublesome patient was liable to be called paralytic.<sup>1</sup> Thus a 60-year old ironmonger remains "motionless and silent . . . like an immovable statue" for many months, though his health and appetite are good; yet Dr. Tuthill says, "from the extreme slowness of manner and dumbness of this patient, I apprehend something of a paralytick nature has already taken place". A sailor aged 22, suddenly taken ill seven months before admission, is "occasionally violent, threatens to hang himself, swears a great deal, is dull and heavy but in good health"; Dr. E. T. Monro then notes that "some suspicion of paralysis is to be attached to this case and more especially as he appears to have been wounded in the head". A lace-maker of 46 becomes weak and tremulous and develops anasarca of her legs: she is reported as "dropsical or paralytick" and is later said "to be approaching a state of paralysis or to have already suffered from it". It is noteworthy that, of the 16 males described as paralytic, three were innkeepers. Four of the 19 cases are said to have had exalted or grandiose ideas and one of these was an innkeeper. Altogether, I think the diagnosis of dementia paralytica can be seriously considered only in 5 cases (though a further 4 cases, of which the notes are perfunctory, could possibly have been paretic). Of these 5 cases, one is under some suspicion on account of his youth (26 years)—another because he was, after a year's stay in the "curable establishment", accepted as a chronic patient (which implies that he had violent or dangerous propensities). I conclude that, although the occur-

<sup>1</sup> There was a rule at Bethlem that patients who developed fits or became paralytic could be discharged immediately as incurable. In the Minutes of Evidence of the Committee appointed by Parliament in 1815 to consider the better regulation of madhouses in England there occur the following curious exchanges, which suggest that a diagnosis of "paralysis" might be no more than a mere administrative convenience. The Committee were questioning Wallet, at that time steward of Bethlem Hospital, concerning the early discharge of patients subject to fits or paralysis. Wallet replied (p. 64):

"—I remember a woman who was discharged as paralytic, who came from Hoxton; the nurses said at the time that she was the strongest patient in the house; she was returned to Miles's.

Do you know Sarah Payne?—Yes.

Was she a strong healthy-looking person?—Very much so.

Was she a violent patient?—She was.

By whose order was she sent to Hoxton?—She was discharged by the medical gentlemen as paralytic.

Had she any paralytic attack during the time she was in the Hospital?—I never heard of any attack.

Had she, in your opinion, the appearance of a person who suffered under paralysis?—I do not know that she had; I saw the difficulty they had in taking her away, in putting on a strait waistcoat; she was very strong."

The matron of Bethlem, Elizabeth Forbes, was also questioned on Sarah Payne (p. 76):

"While she was with you, had she any paralytic attack?—She was much worse when she went back than when she came; she was more violent and unhappy and distressed, always asking if she was going to be murdered and such things; Mr. Haslam thought she was paralytic.

Had she a fit?—I never knew her to have a fit.

No contraction of limbs?—No.

No want of articulation?—No, not at all; but she was always kept handcuffed lately, and chained.

She was sent out in a considerably increased state of violence than when she came in?—Yes, which Mr. Haslam attributed to paralytic (sic.).

Was she very strong?—Very strong; it required three or four people to move her; she was brought to the side-room every day, but there was great difficulty in moving her, she wanted her liberty I believe."

Later still in the Inquiry, Haslam himself was questioned about Sarah Payne (p. 128):

"What became of her?—I do not know; she was discharged from the Hospital; she was paralytic.

She was discharged as paralytic?—She was in a general state of tremor. We apprehended she would soon die; she was incurable. Patients becoming sick and weak, and not being able to undergo the discipline of the house, are immediately discharged."



rence of dementia paralytica at Bethlem Hospital during this period was possible and even probable, it was certainly not common.<sup>1</sup>

<sup>1</sup> Of the nineteen cases stated to be paralytic, the three which seem to me the most suggestive of dementia paralytica are as follows:

(1) Male, age not stated, admitted 18 Jly. 1816.

"Disordered about 5 weeks. Was disordered 2 years ago and recovered. Talks incoherently—not mischievous. Comes from the Parish of New Windsor, played the Serpent in the Earl of Dartmouth's Band. Staffordshire Militia 2 or 3 years ago.

July 20th. A Tremor observable in this case with great incoherence of discourse. 23rd. From the evident tremor of his limbs and lips it is to be feared that Paralytick symptoms may come on in this case.

Aug. 3rd. He imagines that he is the greatest of singers and that he performs at Covent Garden Theatre every night at the present time. 15th. Remains as heretofore. 20th. Either he has already suffered some slight Paralytick attack or the probability is that he will suffer it ere long.

Sept. 10th. Remains in the same condition and is a hopeless case, I fear. 26th. Becomes worse—trembles much and stammers in his speech sometimes—is very much lost in his mind. Has very grand ideas—considers according to Dowie's account that he has four millions of money.

Oct. 30th. He continues to exhibit symptoms of some Paralytick attack which has deprived him of his intellect. He continually harps on his wealth and musical abilities. The use of Calomel keeps him in an equable state.

November. Evident symptoms of Paralysis exist in this case and the grand line of operation appears to be the prevention of any fresh accession of similar attacks. His health is pretty good at this time.

December. The imbecility of mind which accompanies or rather succeeds Paralytick symptoms was never more obvious than in this case. His answers to questions will vary every minute. He will call his wife by 3 different names and give the most incoherent account with a stammering and tremulous voice."

(No further notes.)

(2) Male, age 26, admitted 20.11.1817.

"Disorder'd six months. This is the first attack. He imagines himself a great Commander, being a Jew Lawyer.

Dec. At the latter end of this month, he faulter'd very much in his speech and was evidently partially Paralytick.

Jan. There can be no doubt that some slight degree of paralysis has occurred in this case. The stammering tongue, staring eyes, great incoherence of speech and general demeanour evince this plainly.

Feb. This patient shows repeated proofs of his having suffer'd from some attack of paralytick tendency. His spirits are ever good.

March. He continued very cheerful during this month altho' evidently shattered in his mind and Paralytick. He has an exceedingly good appetite, and is ready to shake hands with everybody. No coherence of speech.

May. It appearing that this patient was altogether paralytick, and that his malady arose solely from this cause, no prospect appearing of rendering him any advantage, he was this day (Discharged as an Improper Object.

(signed E. T. Monro)."

(3) Male, aged 40, admitted 2.7.1818.

"This man has been disordered only 4 months and married only 6 months. He has been 3 weeks at Mr. Pell's Somers Town. He has lived 8 years with Messrs. Rundell & Bridge, Ludgate Hill. He has attempted suicide and is a native of Scarborough. He has a brother who threw himself over Blackfriars Bridge. He had a most excellent character.

Aug. 22. This man has one of the most remarkable craniums Dr. Monro ever saw. There still remains a great propensity to suicide and he appears to be partially paralytick.

Sept. He has an idea that his food and everything else he takes is poisoned. He is a truly deplorable object in every respect.

Oct. A little improvement is observable in this case since the last account. He talks less and is not so much agitated in his general demeanour. He is described as cleanly in his person.

Nov. A very miserable object, decidedly liable to attacks of Paralysis. Stammers in his speech and is extremely confused in his ideas. Very zealous in defence of his master.

Dec. Troubled with a Dyarrhoea about this Period.

Jan 11. Died of Apoplexy.

Appearance observed on examining the Body, 11th Jan. 1819:

All the vessels of the Dura and Pia Mater were loaded with blood. The surface of the latter membrane was copiously moistened with a serous Effusion. The arachnoid coat was thick and opaque over the convexities of the cerebral hemispheres, and the Texture of the Pia Mater generally distended with fluid. The lateral Ventricles were considerably larger than usual and contained an increased quantity of fluid; but they were not distended.

(signed Wm. Lawrence, E. T. Monro)."

Finally, it cannot be without significance that none of Haslam's younger contemporaries credit him with the discovery or even the description of dementia paralytica, although they were certainly well acquainted with his works. Burrows, commenting somewhat sceptically on Haslam's and Esquirol's assertion of the great prevalence of paralysis among the insane, says (1829, p. 175): "In adopting the term paralysis, as it occurs in connection with insanity, we are not sufficiently precise. Paralysis, like apoplexia, comprises very different states of disease."<sup>1</sup> A passage in Prichard's *Treatise on Insanity* suggests that the Bristol alienist's silence on Haslam was not mere oversight. Haslam had resigned his post as apothecary to Bethlem in 1815 but Prichard, writing of general paralysis in 1835 (p. 109), says, "At Bethlem I was assured by the house-steward . . . that he has in many instances recognized the early symptoms of this disease . . . The disease, as it occurred in Bethlem, is characterized by the same symptoms as at Charenton, viz. by imperfect muffling articulation, by tottering in the gait, weakness and inaccuracy in the voluntary movements. Monomania, with pride and the illusive belief in great possessions, is the mental disease which has been noticed in the majority of the cases." In his Croonian lectures of 1849, Conolly not only makes no reference to Haslam but says (p. 38), "it is extraordinary that scarcely a trace, if even a trace of a description of a paralysis, so distinct and peculiar in its character, should be found until we come to the writings of physicians yet living"; but Haslam had died in 1844. Bucknill and Tuke, in their *Manual of Psychological Medicine* (1st edition, 1858) do not mention Haslam in connection with general paralysis, nor for that matter do Falret (1853), Griesinger (1861) or Krafft-Ebing (1866). Baillarger (1860) referred to Haslam's case, but did not attach much significance to it as "very many similarly precise passages have been buried for centuries without being noticed until they were dug up by historians". In 1866 Sankey (p. 178) observes, though without further comment, that "(to Esquirol) is due the credit of attracting attention more pointedly to this disease, though Esquirol himself attributes the merit to Haslam".<sup>2</sup> It is from this time (so far as I can determine) that Haslam's claim begins to be more definitely and generally asserted, not only by English writers (Mickle, 1880, p. 2) but by the French (Bonnet and Poincaré, 1868, p. 4) and the German (Krafft-Ebing, 1894). Yet I cannot but think that the silence of Haslam's contemporaries,

<sup>1</sup> The terms *palsy* and *paralysis* have given rise to some confusion in the history of medicine. They have been used to cover: (a) general enfeeblement of movement arising from any cause (e.g. Willis's "being long fixed in bed"); (b) all degrees of muscular weakness attributable to special disease rather than to general debility (e.g. Parkinson's "shaking palsy"); and (c) complete or nearly complete loss of voluntary power (e.g. Salomon's usage, where the term *paresis* is reserved for partial loss of power). The Parisian physicians who described dementia paralytica were well aware of the semantic difficulty: Delaye in 1824 used the term "paralysie générale et incomplète" and Calmeil (1826, p. 9) adopted the shorter term "paralysie générale" only with reluctance and perhaps because (as Baillarger suggested) it was already in common use.

The term *general* as applied to paralysis was also a source of confusion. See an inconclusive discussion in the *Journal of Mental Science* (1896).

<sup>2</sup> Why, we may wonder, should Esquirol have credited Haslam with a discovery that Haslam's own countrymen denied him? Were it not out of keeping with the magnanimous character of that great Frenchman, we might be tempted to suppose a wish to attenuate the claims of the upstart Bayle, a young man who did not belong to the school of Pinel and Esquirol but had been trained in pathological anatomy by his uncle Gaspard Laurent Bayle and his uncle's friend Laennec. A more reasonable explanation, however, would be that Esquirol, who always thought of paralysis as only a complication of insanity, would have seen no reason to believe that the cases he saw in Paris and which were later delimited by Bayle and Calmeil differed in any fundamental way from other cases of paralysis in the insane already described by Haslam.



who knew and admired his work and who also knew the disease, speaks more eloquently than the historical researches of later times.

Willis and Haslam are, by common consent (at least in English-speaking countries), agreed to have the strongest of the claims put forward for a description of dementia paralytica before the Parisians. I will not, therefore, discuss the claims made for other early writers. Mönkemüller (1911), who studied the subject at the request of Kraepelin, found "only a few cases, mostly very disputable", in the records of the eighteenth and earlier centuries. Among the "Hundred Cases" published by Chiarugi in 1793, Meckel only detected "at least one undoubted case of general paralysis, perhaps even a second"; and Möbius made an interesting observation that during the eighteenth century no famous man died of any illness resembling dementia paralytica, although during the nineteenth century such instances were common—Schumann, Donizetti, Nietzsche and Maupassant, for example (Kraepelin, 1927, pp. 1135 *et seq.*). More noteworthy, perhaps, than the weakness of the positive evidence is the fact that so many able investigators said nothing which can be taken to indicate any acquaintance with the disease. Pinel himself, as late as 1809, when the second edition of his Treatise was published, makes no special mention of dementia in association with paralysis. Yet he was acquainted with Haslam's work (which he praises) and moreover Pinel was, until 1795, Physician to Bicêtre, the Parisian hospital for incurable male lunatics where, if anywhere at that time, dementia paralytica should have been common.<sup>1</sup>

This failure to describe dementia paralytica would—if the disease had been there to describe—be all the more surprising when we take into account the striking clinical syndrome which it commonly presented. Calmeil (1826, p. 326) found the peculiar delusions to be "*infiniment remarquable*". Conolly (1849, p. 39) makes the statement that "of all modifications of mental disorder, the form which is either accompanied from the first with that variety of paralysis which has of late years been observed and described as general paralysis, or eventually supervenes upon such bodily affection, is the most remarkable". Bucknill (1857) says, "The diagnosis of general paralysis is practically of the most facile sort" and "the form of intellectual disorder, moreover, is frequently of the most remarkable kind". Maudsley (1879, p. 432) says, "The group of cases described under this head (general paralysis) unquestionably constitute the most definite and satisfactory example of a clinical variety of mental disease." The egregious characteristics to which these writers draw attention apply principally of course to the grandiose type of dementia paralytica. This type was also called the "classical" type, partly because most of the cases described by Bayle (1826) were of this nature and partly because it was, during most of the nineteenth century, the commonest type.<sup>2</sup>

<sup>1</sup> Browne (1875) says, "It would be difficult to rest satisfied with the belief that, whatever may be the cause, general paralysis did not exist until about 50 years ago, or that it had entirely escaped the cognizance of physicians, general and special; yet it is certain that on examining the works left by Pinel and his predecessors it is impossible to discover any monographic description of this frightful affliction, now so readily detected and diagnosed, although these distinguished men had, for long periods, access to all the experience afforded in Asylums for the Insane." But the Scottish Commissioner in Lunacy cannot have it both ways; either the disease did not exist or it existed but was not recognized.

<sup>2</sup> Between January, 1815 and July, 1823, Bayle (1826, p. 568) collected 189 cases of "chronic meningitis" (i.e. dementia paralytica) among 847 male admissions, and 25 among 606 female admissions to Charenton. His excellent case histories are monotonously similar in their clinical features and no series like them had ever been described before. His patients govern the universe, have 40 million tons of gold, own marble palaces, or build a new paradise. It was, as Bayle says (p. 547), "toujours le même, d'idées dominantes de richesse, de grandeur, de puissance".

The great conceptual advance made by Bayle in 1822 was his belief that the mental symptoms of dementia paralytica and the associated paralysis were both the direct consequence of visible pathological changes in the brain and meninges. We may ask why, if dementia paralytica was always common, such an association between insanity, paralysis and brain change was not noticed earlier. That paralysis was the result of brain change, had of course, long been known, as Willis's cases sufficiently illustrate. The post-mortem examinations made by Chiarugi (Bayle, 1826, p. 383) and Greding (Prichard, 1835, p. 210) showed that vascular engorgement, thickening of the membranes, effusions between the dura and the pia mater and increased fluid in the ventricles were all common findings in the brains of insane patients. No doubt many of these changes were due to agonal infection, prolonged debility, fits, or old head injury; but in the brains of other cases which had shown similar mental symptoms nothing abnormal was to be found. Hence the general opinion arose that post-mortem brain changes were not due to the mental disorder but to its complications—paralysis, phthisis, scurvy, etc. Pinel, according to Prichard (1835, p. 212), "seemed to give up hope of elucidating the pathology of mental derangement by necroscopical research", and this may have been a good reason for his belief (Pinel, 1809, p. 142) that "the primitive seat of insanity is generally in the region of the stomach and intestines and it is from that centre that the disorder of intelligence propagates itself". Esquirol, at least in his earlier years, was of the same opinion and in his article on "Dementia" in the *Dictionnaire des Sciences Médicales*, 1814, says, "The opening of the body teaches us nothing with regard to (the seat of dementia) and all the organic alterations of the brain belong less to insanity than to its complications. I possess many observations on anatomical pathology which, compared with the history of the illness, prove that madness existed before any organic lesion of the brain and that when the organic lesion took place it showed itself by convulsions or paralyzes which are present as complications." Such a view is understandable if organic causes of mental disorder were rare or associated only with simple dementia; but if dementia paralytica had always been common one might have expected that the constant association between its mental and physical signs and its obvious pathological brain changes would have been noticed by the many able investigators who looked for such associations before 1822.

The evidence thus far may be summarized as follows: (1) no very satisfactory or unequivocal accounts of a disease corresponding to dementia paralytica had been given before those of the Parisian alienists in the early nineteenth century; (2) yet by 1823, Bayle found that a fifth of all male admissions to Charenton conformed to his description of—"l'aliénation mentale avec paralysie incomplete par suite de meningitis chronique", while Esquirol (1838, p. 272) gives this proportion in 1826-28 as more than a quarter; (3) in noting the absence of earlier accounts, we must bear in mind not only the striking clinical and pathological features of the disease but also the fact that insanity had been carefully studied during the late eighteenth century from the aspects of nosology and brain pathology. One explanation of these observations is that dementia paralytica, from being a rare or non-existent disease, suddenly became very prevalent in Paris during the second decade of the nineteenth century. It was not recognized before because it had rarely or never occurred before; it was recognized by the Parisian alienists because it became so common there that it could not be missed<sup>1</sup>; it was not thought to be a new disease

<sup>1</sup> This would of course in no way lessen the merit of its first describers. The efflorescence of genius which led to and was evoked by the discovery of dementia paralytica is one of the



because physicians believed that diseases, like species, were enduring and immutable.<sup>1</sup> Another explanation, however, was put forward by Robertson (1923) in his excellent essay on the discovery of general paralysis. He considered that the Napoleonic wars must have produced "a large harvest of cases of general paralysis", many of which would come to the two great mental hospitals of Paris, Bicêtre and Charenton (the latter catering particularly for army officers). These hospitals had been re-organized by or under the influence of Pinel, who had introduced kindness and orderliness into the regime and insisted on full and careful case-records. "The symptoms of general paralysis", says Robertson, "are so striking that the great number of similar cases thus collected together could scarcely have been overlooked when Pinel's method of caring for the insane was adopted." This may be conceded and is not incompatible with the first explanation; but, unlike the first explanation, it does not account for the later history of dementia paralytica and for the evidence which suggests that, from its origin in northern France, the disease spread in a fairly well-defined manner across Europe, then to America and later still to less highly industrialized countries.

## PART II

The earliest definite reference to dementia paralytica in France is, I think, that of Esquirol, who in 1814 wrote: "When paralysis is a complication of dementia, all the paralytic symptoms appear one after the other; first of all, articulation of sounds is laboured; soon after locomotion is made with difficulty; finally, there is loss of control of the excretions." The disease was certainly common at Charenton in 1816, when the cases described by Bayle began to be admitted; and we have Esquirol's word for it that by 1828 one-sixth of all admissions to Charenton were parietic and the disease was common at

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most astonishing and glorious chapters in psychiatry. Baillarger (1860) considered this discovery the most important single achievement in the history of mental disease; Harrington Tuke (1859) wrote of Calmeil's *De la Paralyse* that it described general paralysis "with a terseness and success that may be considered as rendering his work unrivalled in medical literature". Robertson is no less emphatic: referring to the publication in 1826 of Bayle's *Maladies Mentales* and Calmeil's *De la Paralyse*, he says—"The appearance in the same year of two such books . . ., both dealing with a newly discovered disease in so masterly a fashion, is unique in the history of medicine. And, although much has been written about general paralysis during a century, the disease is described in these two books so fully, so faithfully and so convincingly that future additions to our knowledge seem little more than details. No other book devoted to this subject alone was written for two generations afterwards, nor was there any needed." I wish I could add the commendation of some *general* physician.

<sup>1</sup> We might even hazard the guess that the honour of being the eponymous discoverer of dementia paralytica went to Bayle because, not being a pupil of Esquirol and having no great experience of mental disease, he saw his patients' behaviour without the preconceptions of instruction or of habit. Bayle was only 19 when he became interne under Royer-Collard at Charenton, and only 23 when he submitted his inaugural thesis—"Recherches sur les maladies mentales" (1822). But Georget, Delaye, Falret and Calmeil would be thoroughly familiar with the classification and opinions of their great teacher, Esquirol, and of *his* great teacher, Pinel; they were for many years unable to conceive that paralysis could be other than a mere epiphenomenon of insanity, as scurvy or phthisis might be; and Esquirol himself never abandoned that view (Baillarger, 1859, 1860). "There is a suspicion", says Robertson, "that antagonism to Bayle existed because he did not belong to the school of Esquirol." This is too mild. It is obvious that intense passions were aroused. Esquirol's pupils went out of their way to pour scorn on Bayle's ideas and to belittle his achievements. According to Toulouse (1922), even Pinel pronounced his work "premature and useless". We read with sorrow but without surprise that after his term of office as interne at Charenton ended in 1823, Bayle "drifted away" from the study of mental diseases to that of general medicine, anatomy, medical history and (*horresco referens*) bibliography. He died in 1858, two years before the writings of Baillarger convinced his compatriots that dementia paralytica might properly be called "la maladie de Bayle".

Bicêtre and at the St. Yon asylum near Rouen (quoted by Prichard, 1835, p. 101). Yet it remained rare in the south of France (Esquirol, 1838, p. 273): between 1822 and 1825 Rech found no case among 132 admissions of insane patients to the hospital at Montpellier; in Toulouse, Delaye found only five cases among 111 patients (no date given); while in north Italy it was rarer still, as Esquirol himself confirmed in 1834. Even in 1849, Lunier concluded from personal observation that dementia paralytica was rare in the south of France. Yet by 1876 it must have become common, for we read that "in the south of France, if we may judge from the official returns, general paralysis has greatly increased during the last generation or two and at present is nearly equal to that in the north" (Eighteenth Report of the Commissioners in Lunacy for Scotland).

Two further observations may serve to suggest that for many years dementia paralytica was uncommon except in the environs of Paris. Salomon (1862) states, "France is the peculiar focus . . . Paris is the headquarters of the disease." Krafft-Ebing (1866) gives a list of the literature concerning dementia paralytica "from the earliest up to the most recent date" and has no reference to any but French writings until 1848. He missed some of the English literature but he is unlikely to have missed any German work.<sup>1</sup> The absence of early German references suggests that dementia paralytica was too rare in that country for the French descriptions to arouse much interest. This is confirmed by Mönkemüller's study (1911) of the case records preserved from the penitentiary and madhouse at the town of Celle, near Hanover. The records cover the period 1750 to 1831 and among 669 cases, Mönkemüller found 31 resembling dementia paralytica. They were distributed over the years as follows:

|           | Years |    |    |    | Admissions | Cases Resembling<br>Dementia Paralytica |
|-----------|-------|----|----|----|------------|-----------------------------------------|
| 1750-1800 | ..    | .. | .. | .. | 211        | 0                                       |
| 1801-1810 | ..    | .. | .. | .. | 153        | 6                                       |
| 1811-1820 | ..    | .. | .. | .. | 188        | 15                                      |
| 1821-1830 | ..    | .. | .. | .. | 117        | 10                                      |

The diminished number of cases in the last decade is probably accounted for by Mönkemüller's observation that many cases were then being diverted to a new hospital at Hildesheim. It is of interest, too, that "a relatively large number" of the 31 cases were soldiers and had therefore probably been in conflict with Napoleon's armies.

In England, Burrows (1829) seems to have been the first to comment on the new disease. He refers to the descriptions of Georget, Bayle and Calmeil, and then (p. 177) remarks on the "singular discrepancy" in the prevalence of paralysis complicated by insanity in the French as compared with the English hospitals. In the latter, "from inquiry I know the number is comparatively trivial . . . In my own practice, the proportion has not been one in twenty." Conolly (1830), in his *Inquiry concerning the Indications of Insanity*, makes no mention of paralysis in spite of a reference to Bayle's "excellent work".<sup>2</sup>

<sup>1</sup> Meyer (1959) has pointed out that Griesinger, in the first edition of his textbook, 1845, drew attention to the occurrence of "so-called general paralysis" in Germany.  
<sup>2</sup> Conolly confirms Bayle's observation that many patients dying of consumption show "spes phthisica". The reference is not, of course, to the pathologist Gaspard Laurent Bayle, who wrote the famous *Recherches sur la phthisie pulmonaire*, but to Gaspard's nephew Antoine and his *Maladies du Cerveau* (p. 551).



Prichard (1835) went to some pains to determine whether Burrows's opinion was correct but (p. 108) he "met with considerable difficulties in obtaining satisfactory information". He concluded, however, that the disease was "comparatively rare in private asylums" and, in the one public asylum (Gloucester) for which he gives figures, only 16 cases had been observed since 1828. Yet by 1849 the situation must have changed, for Conolly in his Croonian lectures says that general paralysis was common in all the asylums of England, France, Belgium and Germany, though rare in Italy and Spain. We may consider, too, the progress of the disease in one particular asylum, the Middlesex Lunatic Asylum at Hanwell, from figures given by its superintendents. Sir William Ellis makes no mention of dementia paralytica in his *Treatise on Insanity* of 1838. Two years later Millingen (1840) finds only twelve cases of paralysis among 1,000 patients and contrasts this with the high prevalence at Charenton. By 1849, however, Conolly finds that among 690 deaths at Hanwell over the last ten years, the proportion of those due to general paralysis was 37 per cent. in males and 11 per cent. in females. These figures for a London asylum were probably well above the average for the country, as in 1876, when the annual reports of the Commissioners in Lunacy first give separate statistics, the proportion of deaths from general paralysis in all the asylums of England and Wales was 14 per cent. in males and 3 per cent. in females.<sup>1</sup>

The disease does not seem to have appeared in Scotland until 1839, nor was this due to lack of knowledge of it. "I saw the disease in Paris in 1832", says Browne (1875), "but did not recognize it in this country till 1839." It soon became fairly common in Edinburgh and Glasgow (Workman, 1858) but elsewhere remained rare or unknown for many years. Thus Skae (1860) says that his former pupil Howden, who had been well acquainted with the disease in Edinburgh, could not find a single case among the 300 patients of the Montrose Asylum; and during the years 1869 to 1872, among 200 admissions to the Fife and Kinross Asylum, Batty Tuke discovered only four cases (Bucknill and Tuke, 1874, p. 127). As late as 1879, Maudsley could remark that general paralysis was "hardly ever met with in the highlands of Scotland". In that same year, however, the proportion of deaths due to general paralysis in all the asylums of Scotland was officially given as 18 per cent. in males and 3 per cent. in females.<sup>2</sup>

In the United States, dementia paralytica was not recognized until after 1840. I have been unable to consult the original reference of Luther Bell (his Annual Report for the McLean Asylum, Boston, 1843), but that he was the earliest to record the disease is confirmed by several writers. Thus Bucknill and Tuke (1874, p. 323) say: "The late Dr. Bell of America, writing in 1844, said it was only within three years that patients had been admitted to the McLean Asylum labouring under general paralysis. On looking over the register for the past years he could not find a case the description of which resembled

<sup>1</sup> Nevertheless, in some asylums in England and Wales there were whole decades when a quarter or more of all the male admissions were paretic. These cases pursued a slow but relentless course to complete dementia and death, and it is not hard to imagine that the unrewarding and dispiriting task of nursing them was one reason why the high standards of humane care set up by the pioneers of non-restraint and moral management seem gradually to have deteriorated during the latter half of the nineteenth century.

<sup>2</sup> See the 41st Annual Report of the General Board of Commissioners in Lunacy for Scotland (1899, App. A, Tab. X). We may calculate a crude mortality rate for general paralysis in England and Wales and in Scotland, using the figures given in the Board of Control Reports for the year 1876 and the estimated population of the two countries in this year. Expressed as deaths per million of the population, the figure for England and Wales is over 50, for Scotland it is under 20.

the manifestations so graphically described by many English and Continental authors." Chase, writing in Philadelphia in 1902, says (p. 21): "As an illustration of the former rarity of the disease in this country, it is said that the eminent alienist, the late Dr. Luther Bell, of Massachusetts, at the time of his first visit to England about fifty years ago, had never recognized a case of general paresis, a statement which seems almost incredible considering its rapid increase and spread in late years, especially during the past quarter of a century." There was no further report of cases of general paresis in the States until that of Pliny Earle in 1847 (MacDonald, 1877; Wagner, 1902). Recognition was even more tardy in Canada. "When I entered the Toronto Asylum in 1853", says Workman (1858), "there was not a single case, as far as I could judge, in the institution but it was not long before it began to make its appearance." That there was a characteristic mode of spread of the disease suggested itself very strongly to his fellow-countryman MacDonald (1877).<sup>1</sup> MacDonald says, "A curious point in the history of the disease is its gradual extension from one country to another and its gradual increase in localities where it has once appeared"; and he gives a table of asylum reports indicating that general paresis was still rare in the western and southern states compared with its prevalence in the central states and those of the eastern seaboard. In his own institution (the New York State Asylum) the numbers of paretics were increasing annually and although some of the increase might be explained by familiarity, yet "when all due allowance is made on this account there is still abundant evidence that the disease is steadily and rapidly extending". His observations led him to believe that in any one place the disease progressed in a manner shown by: first, its appearance and recognition in males; then, increased frequency in males and its appearance in females; increased frequency in both sexes with an increased proportion in females; and finally, changes in the nature of the disease, such as its duration and the age of patients attacked. He also quotes figures to show that dementia paralytica was at that time much more prevalent in Britain than in the United States; in 1874-76, for example, the percentage of cases in the asylums of Great Britain was 14.1 for males and 3.2 for females whereas in the U.S.A. the figures were 4.1 and 0.4. Workman had reached similar conclusions in 1878. Observing that there

<sup>1</sup> Macdonald, Workman and Mickle were Canadians and had all studied at the Toronto School of Medicine. Mickle, who emigrated to England and became Superintendent of Grove Hall Asylum, London, was unimpressed by the American statistics of his two compatriots and dismissed them with the remark that "many statistics are utterly misleading . . . merely an index of the varying capacity of medical men to recognize the disease". But when we remember that this disease was recognized in America only at a time when every psychiatrist must have been familiar with its textbook description, and that the progress of any infectious disease across that vast and largely unopened continent must have been relatively slow, we may think the Americans had a better opportunity than Europeans of observing the spread of dementia paralytica.

Another statistical sceptic was Spitzka, professor of medical jurisprudence at New York, and originator of the maxim that general paresis was due to the three W's—wine, women and worry. He severely disapproved of "the widely circulated error" that general paresis was "travelling" from east to west of the American continent. His opposition to MacDonald's statistics was based (1883, pp. 183, 208): (1) on the fact that in the German and French asylums, "where the diagnostic acumen of the medical officers is unquestionable", the disease was said to be increasing only very slightly; and (2) on the *ad hominem* argument that MacDonald had not only attempted to support the ridiculous theory of the Englishman Austin that in general paresis an affection of the left pupil was associated with mania and of the right with depression, but that he had got this association the wrong way round, so that his figures instead of supporting Austin's theory were at complete variance with it—a careless error which, says Spitzka, "constitutes a significant commentary on the reliability" of the author's work in general. Yet in fact it was not MacDonald but Spitzka who was the careless one, inasmuch as Austin (1859, p. 31) claimed mania to be associated with contraction of the left, MacDonald (1877) with dilatation of the right pupil.



were markedly fewer paretic deaths in the Toronto Asylum during the eighteen-seventies than in English asylums of comparable size, he adds, "I have carefully examined over 130 reports of United States and Canadian asylums for the last 3 years. In more than half of this number I have found that paresis was either totally unmentioned or but very exceptionally noted in the obituary tables. I believe it is a recognized fact that in the Southern and farthest Western States the disease is unknown; or at least it has been unnoticed . . . To an English superintendent, who numbers his paretics by the score and shows a paretic death proportion of one in three or four, this fact could not fail to appear marvellous." During the next twenty years, however, dementia paralytica spread and increased in both Canada and the States, so that by 1894 Ballet and Blocq could write, "Central and Western Europe and North America have the unhappy privilege of furnishing the greatest number of cases." Dayton's figures (1940, p. 468) show that, of first admissions to the mental hospitals in the State of Massachusetts between 1917 and 1933, the proportion of paretics was 10.6 per cent. for males and 3.0 per cent. for females.

The spread of dementia paralytica among the negro population of North America is also worth noting. Long after it had become common among whites, the disease was still rare in negroes. As late as 1883 and 1886, asylum superintendents in North Carolina and in Georgia could claim never to have met with general paresis among their coloured patients (Moreira and Penafiel, 1907). In the New York Asylum, Spitzka (1883, p. 180) found the proportion of cases lower among negroes than among whites and indeed used this finding to support his belief that general paresis was "more frequent with races of a high than of a low cerebral organization". Berkley, in 1893, drew the same conclusion for the Northern States generally; but a few years later, in his *Textbook on Mental Diseases* (1900, p. 194), he writes of dementia paralytica in the negro: "Before the civil war and for some few years afterwards the disease was unknown among them. Little by little the number of cases grew in frequency. Such patients were at first regarded as curiosities, but at present in Baltimore paretics represent approximately the same percentage, according to the total population, in negroes as they do among Caucasians; nor do the general types of the disease differ materially in the two races." Emil Kraepelin (1913) quotes an investigation "very kindly undertaken for me by Hoch in New York" which showed that in seven large asylums the average rate for paresis in negroes was over twice that in whites. Green (1914) wrote, "For many years it was claimed that general paresis was seldom met with in the negro race. That this claim is untrue is generally accepted today"; at the Georgia State sanitarium he found the proportion of general paresis among negro admissions was twice that of the whites. Plaut, in 1926, again found a higher rate of general paresis among negroes than whites in America, and in the same year Kraepelin (1926) lent the weight of his authority to the "remarkable fact" that general paresis had been extraordinarily rare in North American negroes forty to fifty years earlier but was now very common among them. Figures quoted for Massachusetts mental hospitals from 1917 to 1933 by Dayton (1940, p. 411) and for New York State Hospitals in 1935 by Rosanoff (1938) indicate that general paresis continued at least twice as common among negroes as among whites; while recent work (Malzberg, 1953) indicates that in New York State this comparative factor has risen to more than five.

The spread of dementia paralytica in certain other countries may be mentioned more briefly. In Ireland, the disease was generally acknowledged to be rare at least up until the eighteen-seventies. Thus Ashe (1876) found no cases

in the asylums of Belfast or Cork and only one in Londonderry and drew the conclusion that "general paralysis is scarcely to be found in Ireland". Deas, in 1879, echoes "the undoubted fact that general paralysis is all but unknown in Ireland", and seven years later Mickle (1886, p. 259) can still say that "Ireland enjoys an extraordinary immunity from general paralysis". Yet the Reports of the Inspectors of Lunatics (Ireland) in 1890 (the first year in which separate figures are given) indicate 30 deaths—more than 3 per cent.—from general paralysis, a number and proportion which increases in later years. In the Isle of Man, the immunity to the disease seems to have lasted even longer, Richardson (1891) reporting that "during the past six years I have seen no instance of it in a patient of Manx parentage", though two cases had occurred in immigrants. In Denmark, figures given by Heiberg (1932) suggest that dementia paralytica was uncommon there until the late eighteen-sixties. The number of paretic deaths at the St. Hans Hospital, Copenhagen, in 1866 was five; but the average annual deaths for the decades from 1866 until 1925 were 8.6, 14.0, 23.1, 35.8, 41.3 and 51.7. Heiberg also gives reasons for believing that the figures represent "with a rather high degree of accuracy" the actual number of paretic deaths in the city of Copenhagen. Smith's figures (1926) for admissions to the Kommune Hospital in Copenhagen from 1876 to 1926 show the same general trend (Table I).

TABLE I

*Numbers of Cases of Dementia Paralytica Admitted to the Kommune Hospital, Copenhagen (from Smith, 1926)*

| Year      | .. 1876<br>-80 | 1881<br>-85 | 1886<br>-90 | 1891<br>-95 | 1896<br>-1900 | 1901<br>-05 | 1906<br>-10 | 1911<br>-15 | 1916<br>-20 | 1921<br>-25 |
|-----------|----------------|-------------|-------------|-------------|---------------|-------------|-------------|-------------|-------------|-------------|
| Males     | .. 88          | 138         | 139         | 188         | 202           | 222         | 169         | 316         | 308         | 305         |
| Females   | .. 3           | 23          | 37          | 57          | 89            | 104         | 97          | 149         | 121         | 116         |
| Ratio M/F | 29             | 6.0         | 3.8         | 3.3         | 2.3           | 2.1         | 1.7         | 2.1         | 2.5         | 2.6         |

Similar trends are to be found in reports from other countries. In Brazil, according to Moreira and Penafiel (1907), there were five cases of paresis admitted to the National Hospital for the Insane in Rio de Janeiro in 1889; but the average annual number admitted during the 3 quinquennia from 1890 to 1905 was 10.1, 17.4 and 21.2, while the percentage of paretic admissions increased from 3.1 to 4.0 and 5.3. They also observe that the disease was commoner in immigrants than among natives, a differential prevalence which held true of other countries until quite recent times. Thus Lennox (1923) observes that although syphilis was three times as common in China as in America, the incidence of neuro-syphilis was less than one-seventh as great; and he quotes "writers of experience" who, during the years 1907-1916, hardly ever saw general paresis in Chinese, and where it occurred the patient was found to have been infected from a non-Chinese source. Although Lennox thought the rarity of neuro-syphilis among the Chinese might to some extent be due to lack of facilities for diagnosis, yet he concluded that this would "probably not account for all the observed racial differences". Stewart (1924) quotes a report by Christidis of 1922 that among 3,000 cases of syphilis in Persia he did not find a single paretic; paresis was also rare in European residents who had acquired syphilis in Persia but was common in those infected from outside sources.

The general facts related above always appeared sufficiently remarkable to contemporary workers to demand an explanation. Before considering some



of the earlier explanations, I will suggest that these facts seem broadly explicable on the hypothesis that a mutant neurotropic strain of the syphilitic spirochaete appeared in northern France and then spread by venereal infection along the trade routes of the world. On this hypothesis, the new disease would tend to spread first to those countries having the closest commercial intercourse with the country of origin; and on reaching a new country overseas, would appear first in the port towns and only later spread inland. Again the disease would tend to spread more quickly among peoples of similar cultural and ethnic group and only move slowly to other groups. The facts that dementia paralytica is a chronic disease and that a variable interval of five to twenty years separates the initial infection from the appearance of symptoms would account for the absence of any explosively obvious outbreak of cases. Such an epidemiological hypothesis could hardly have been put forward before 1913 as until then the infectious nature of dementia paralytica was unsuspected or unproved; and by 1913 the disease had become fairly evenly distributed over the civilized world and it was easy to dismiss the older statistics as valueless because they had not been based upon objective methods of diagnosis.

The diagnosis of dementia paralytica became objective during the years 1896 to 1912, when the specific reactions of the cerebrospinal fluid were elucidated by Babcock, Alzheimer, Wassermann and Lange. Before this, diagnosis during life had to be made entirely on clinical grounds, though post-mortem examination added much to the accuracy. (It is worth noting that, according to the reports of the Commissioners in Lunacy, the proportion of post-mortem examinations carried out on patients dying of general paralysis in the asylums of England and Wales between 1901 and 1911 was over 70 per cent. We have no post-mortem figures for earlier years, but no reason to suppose they were less.) No doubt in the statistics of dementia paralytica were included some cases of arteriosclerotic, alcoholic and epileptic dementia, cerebral syphilis, cerebral tumour, pellagra and plumbism; but it had been recognized almost from the start that these conditions entered into the differential diagnosis, while conditions that were differentiated only later, such as the dementias of Pick and Alzheimer, were too rare to be of statistical importance. No doubt, too, the diagnosis was made more carefully in some centres than in others, but this is true of all diseases. The consequence would be that the edges of the statistical picture were blurred by a penumbra of misdiagnoses and the problem is—whether the size of this penumbra was such as to fog the true picture beyond recognition.<sup>1</sup> In assessing the value of these nineteenth-century statistics, it is perhaps useful to reflect that the diagnosis of dementia paralytica at that time was probably much more accurate than is the present day diagnosis of schizophrenia,<sup>2</sup> for the former disease presented not only mental changes

<sup>1</sup> Kraepelin (1927, p. 1137) discusses the unreliability of the nineteenth century statistics on dementia paralytica and gives his opinion that "they are set about with so many sources of error as not to allow any definite conclusion on the actual alterations in frequency of the disease". Nevertheless, he in fact permitted himself to draw general conclusions: for example (p. 1145), "from these considerations we may take it as very probable that dementia paralytica was formerly uncommon, then underwent a progressively rapid increase from the beginning of last century and for some time now has been gradually diminishing"; and again, discussing the sex incidence (p. 1150), "although the figures may be considerably influenced by the sources of error mentioned above, yet there can be no doubt of the overall increase in the danger to the female sex from dementia paralytica".

<sup>2</sup> It is sometimes urged that the present-day diagnosis of schizophrenia is too uncertain for epidemiological studies of this disease to be meaningful. The history of dementia paralytica suggests that we should be unwise to neglect such studies. In 1857, Esmarch and Jessen had drawn attention—rather apologetically—to the statistical relations between syphilis and paresis. Another early piece of evidence for the syphilitic hypothesis was provided by Sankey,

but physical signs and characteristic post-mortem appearances and was uniformly fatal within a few years. Although it seems probable that before 1906 there was some degree of confusion as to what should be included in the diagnosis of dementia paralytica, yet I cannot find that, on the whole, there was any sudden fluctuation in the reported incidence or mortality of the disease after the introduction of objective methods of diagnosis.<sup>1</sup>

It is a curious historical fact that during the nineteenth century each generation of psychiatrists was confident of its own ability to diagnose dementia paralytica but was very ready to doubt the diagnostic accuracy of its predecessors. Thus an anonymous reviewer of the 41st Annual Report of the General Board of Commissioners in Lunacy for Scotland (*Journal of Mental Science*, 1907), referring to the continued increase in admission rate and deaths of general paralysis during the past 25 years, says: "The reviewer is convinced that a few years ago many of the cases now returned as having died from general paralysis would have been described as cases of cerebral softening, disseminated sclerosis, and cerebral paralysis."<sup>2</sup> Twenty-one years before this, Mickle had

who, in 1866, pointed out the close association between the incidence of syphilis and of paresis in different social classes. But this delicate flower was withered by the scorn and authority of Mickle, who, in his textbook (1880, p. 105) dismisses it with the inappropriate remark that "even if true this does not establish any connection between the syphilis and the general paralysis". Krafft-Ebing, on the other hand, was so impressed by the statistical evidence that he was emboldened in 1894 to inoculate nine paretic patients with syphilis; but, as Berkley (1900, p. 174) and others observed, this proved nothing, for persons infected with syphilis do not necessarily develop symptoms, patients with longstanding syphilis may acquire the infection anew, and other investigators (see Diefendorf, 1906) repeated Krafft-Ebing's work with contrary results. Yet this doubtful experiment caught hold of the popular fancy, convinced many who had been sceptical of all the patiently accumulated statistics, and is still regularly quoted as one of the landmarks in the history of dementia paralytica.

<sup>1</sup> The difficulties of clinical diagnosis were indicated by the problem of "pseudo-paralysis" (see, for example, Hyslop, 1896). It is likely that these difficulties increased at the end of the nineteenth century on account of the rapid changes in the proportions of the different clinical types of dementia paralytica. However, it seems that the difficulty lay more in the initial than in the final diagnosis: Kraepelin says of the period 1892-1907, "at that time we had the tendency to diagnose the condition as early as possible from the clinical picture. . . . Consequently we made many wrong diagnoses later discovered by regular follow-up" (1927, Vol. I, p. 958).

Objective diagnosis became common after Wassermann's demonstration, in 1906, that his complement-fixation test was given by the cerebrospinal fluid of paretics; and was further refined after 1912 when Lange discovered the specific reaction of the fluid to colloidal gold. With these facts in mind we may note that in England and Wales:

1. The Registrar General's figures from 1901 onwards for deaths due to general paralysis of the insane show no change other than a continued downward trend (Fig. 2);

2. The change in sex ratio of deaths from general paralysis of the insane is closely paralleled by that from tabes, the accurate diagnosis of which was probably little influenced by the new techniques (Fig. 1);

3. First admissions to asylums of cases diagnosed as general paralysis of the insane are recorded in the annual reports of the Board of Control. These show a sudden decrease in the numbers in both sexes for 1914, an occurrence which may be attributed to the outbreak of the first world war; otherwise, neither the numbers nor the sex ratio show any sign of short term change between 1900 and 1928.

<sup>2</sup> This reviewer seems to have been particularly unguarded in his assertion. The Annual Report gave a table of deaths, not only from general paralysis but also from "apoplexy and paralysis" and the numbers in this latter table did not vary over 30 years and showed no sex difference: clearly the Scottish doctors had been at pains to separate "cerebral softening" and "cerebral paralysis" from general paralysis. As for disseminated sclerosis, the Reports of the Commissioners in Lunacy give the number of deaths in England and Wales from cerebral and spinal sclerosis in 1901 as 8, in 1906 as 18, in 1910 as 9; the number in Scotland would be proportionately less and it seems clear there had been little variation in the statistically negligible number of such cases. Again, a fellow-reviewer writing twelve years earlier on the 36th Annual Report (*Journal of Mental Science*, 1895) had said, "There can be no reasonable doubt, even after making due allowance for possible greater certainty in diagnosis, that of late years there has been a steady and by no means inconsiderable increase (in general paralysis), notably in the male sex."



written (1886, p. 248), "It is difficult to say how far the apparent increase of general paralysis among women of late years is due to a former defective recognition of it and faulty diagnosis, owing to the less salient features and less dramatic course of general paralysis as it occurs in women than as in men." Twenty-six years before this, Skae (1860) had said,—"for many years (general paralysis) must have been imperfectly known and recognized even in large asylums, if we may judge from the small proportion of cases mentioned in the annual reports of these asylums, compared with the large number which now figure in the tables of these reports. The only other explanation of this fact is that the disease has been increasing in frequency in this country of late years." And twenty-five years earlier than this, Esquirol (1838, p. 274) took Burrows to task with the words: "This worthy writer attributes the frequency of paralysis in Paris to our bad management and our failure to take proper precautions in guarding our insane from exposure to inclement weather; whereas in England, he says, the patients are very well cared for . . . I am convinced that once the symptoms of paralysis complicating insanity are better understood, there will be found in England and particularly in London as many paralytic insane as there are in Paris."

Although the statistics of earlier authors could always be dismissed as unreliable, yet the reported variations in the prevalence of dementia paralytica at any one time could not be so dismissed, because they were again and again confirmed by experienced psychiatrists from personal observations.<sup>1</sup> Of the explanations offered, however, none was adequate and many were self-contradictory. The lower consumption of alcohol was held by Lunier (1849) to account for the lower prevalence of dementia paralytica in southern France; by Wise (1869) for the "remarkable rarity" of the disease among the natives of India; and by Kraepelin (1913) for its rarity in upper-class European women, in "non-Europeanized" peoples and in Mahomedans. Yet this explanation would certainly not account for the low prevalence of dementia paralytica in Northern Scotland and in Ireland, nor for the observation that "the Irishman has to go to America to be attacked by it, for at home he seems immune" (Berkley, 1900, p. 193). Clouston (1883, p. 379) considered "hard muscular labour" was among the exciting causes of dementia paralytica, yet Maudsley (1879, p. 433) attributed its rarity in Scottish highlanders to their taking "a great deal of bodily exercise". An attack of malaria or relapsing fever soon after syphilitic infection has been held to account for the rarity of dementia paralytica in the tropics, but McCartney (1946) has pointed out that neuro-syphilis is rare in the Marshall Islands where there is no malaria; and malaria would not explain the rarity of dementia paralytica in many colder countries such as Ireland and Norway. Towards the end of the nineteenth century the association between syphilis and dementia paralytica became increasingly well-established and the importance of the former as an exciting cause of the latter disease was summed up in the famous "civilization and syphilization" aphorism of Krafft-Ebing at the Moscow Congress in 1897. But as Mott pointed out in

<sup>1</sup> One of the strongest objections to the Theory of Evolution was that, as no one could see evolution taking place, the theory was merely a hypothetical explanation of events long past and incapable of proof or disproof; and a recent demonstration that the evolutionary process can actually be observed today in certain species of seabirds has been claimed as valuable additional evidence. In the same way, many nineteenth century psychiatrists found it hard to believe that the prevalence of dementia paralytica in different countries could have changed significantly during the century; but its rapid increase among American negroes, a phenomenon that took place under the very eyes (so to speak) of Kraepelin, was a practical and almost irrefutable demonstration that such changes could occur.

1900, dementia paralytica was rare in some countries (Persia, Japan, Egypt) where syphilis was very common, a fact with which Kraepelin (1913) concurred and which he was at a loss to explain. The belief that "civilization" was a factor determining the prevalence of dementia paralytica had long been held, though there was disagreement whether the effects were due to the excessive sensitivity of more highly civilized beings or to their degeneracy. Salomon (1862) thought the peculiar susceptibility of Frenchmen to the disease was the result of their "insatiable thirst after 'la gloire' ". Mickle (1880, p. 97) taught that "a life absorbed in ambitious projects, with all its strenuous mental efforts, its long-sustained anxieties, deferred hopes and straining expectation . . . chagrins, forced erethism of the intellectual faculties . . . exposure to constant sources of annoyance—all these predispose to general paralysis". Stewart (1896) considered the recent increase in the disease as due to "increasing moral and physical decadence, lessening power of resistance and diminishing vitality, and increasing tendency to premature and rapid racial decay"; though a few years later (1901), when subsequent figures indicated a slight fall in the number of paretics, he was happily able to conclude that the tendency to racial decay in England and Wales had undergone a reversal.<sup>1</sup>

Kraepelin (1913, 1926, 1927) was much occupied with the problem presented by variations in prevalence of dementia paralytica in different countries. When in Java in 1904, he had been unable to discover a single case among the natives and he did not believe that the reported variations in prevalence could be explained by variations either in the prevalence of syphilis or in the recognition and diagnosis of paresis. He admits that the theory of a special strain of syphilis would explain the otherwise very difficult fact that dementia paralytica is rare in some countries where syphilis is common but he rejects this theory on two counts. The first count is that "we see Europeans become paretics after infection with the same syphilis to which the nervous tissue of the natives is immune". He gives no reference for this statement and it would clearly never be easy to establish that a European acquired syphilis from a native rather than from an immigrant or in another country. The second count is that "in Constantinople the different races show a very different susceptibility for paresis although the syphilis of the Turks, Greeks, Jews and Armenians is certainly the same". From this statement it would appear that Kraepelin conceived of different strains of syphilis being statically distributed in different countries and that he did not have in mind the concept of a new

<sup>1</sup> Nineteenth century ideas on the aetiology of dementia paralytica provide material for a historical study which might illustrate our contemporary views on a disease such as schizophrenia where the aetiology is still obscure. Not only do many of these ideas seem very strange to us now, but they led to the advocacy of "rational" methods of treatment and prevention which might seem even more strange were it not that the history of medicine is full of such things. For example, the hypothesis that dementia paralytica was caused by sexual excess led to the prophylactic advice that wives should be "cautioned against being too loving to their lords" (*Journal of Mental Science*, 1873). Of course, not everyone agreed with such a view; Mickle (1880, p. 105) was contemptuous of it, on the grounds that married women were not lascivious bacchantes and stood in no need of such advice.

For a long time, one of the most unlikely of these speculations was that dementia paralytica was due to syphilis. The statistical and epidemiological evidence in favour of this view, however, became increasingly strong at the end of the nineteenth century. But statistical evidence is never proof and as late as 1902 Nonne could state that in his opinion "progressive paralysis is not a specific syphilitic disease of the brain". Kraepelin, in 1904 (and this was two years before Wassermann showed that his antigen reaction was given by the spinal fluid of paretics), was bold enough to commit himself absolutely to the syphilitic hypothesis, but for the more cautious or less statistically-minded psychiatrist there was no sure path through the speculative labyrinth until the autumn of 1912, when, in the paretic brain sections sent to Noguchi by Moore, the pale visage of a few spirochaetes sufficed to disinherit chaos.



strain in the process of spreading from Europeanized to non-Europeanized countries; yet it is on this latter concept that most of the facts seem explicable.

The same belief in a static distribution of a neurotropic strain is evident in Kinnier Wilson's writings. In his *Neurology* (1941, Vol. I, p. 462; 2nd edition, Vol. I, p. 485), he states: "Another allegation, often quoted by those who believe in the dualist theory, is to the effect that in certain countries where syphilis is rife, neuro-syphilis is conspicuous by its relative absence . . . But most of such claims are proving visionary in the light of advancing knowledge. In 1926 Plaut showed that the incidence of general paralysis among American negroes is actually higher than among whites." Wilson seems here to be supposing that the earlier statistics on the scarcity of dementia paralytica in negroes were simply false. He was not alone in such a belief, for there are many references in the literature to the "legend" that dementia paralytica did not occur or was very rare in certain communities and to the "advancing knowledge" which showed such legends to be false (see, for example, Barnes, 1891, quoted by Moreira and Penafiel, 1907; Samuels, 1916; Marie, 1922). Yet Kraepelin definitely rejected the "legend" theory,<sup>1</sup> and it would seem altogether more reasonable that real increases in the prevalence of dementia paralytica occurred; and it would then be at least as satisfactory to explain these increases in terms of the spread of a neurotropic strain as by such vague hypotheses as "unknown protective influences" or "factors incidental to civilization" (Wilson, *op. cit.*, pp. 536, 486).

#### CHANGES IN SEX RATIO

From the time of its discovery, dementia paralytica has always appeared to be more common in men than women, but the figures given for the proportion of male to female cases have varied widely in different times and places. "The comparative figures can vacillate between one to two and one to seventeen or even higher values", said Kraepelin (1926); he thought the variation could not be attributed to sex differences in the incidence of syphilis but, apart from suggesting that a low consumption of alcohol might account for the rarity of the disease in upper-class European women, he offered no explanation. The statistics have been discounted as fallacious but otherwise there has not, as far as I know, been any general attempt to explain these variations in sex ratio.

In hazarding a partial explanation, I suggest that if factors of time and place are taken into account it becomes possible to discern a fairly constant pattern of change, similar to that suggested by MacDonald in 1877, viz. that when dementia paralytica first appears in a country the sex ratio (males to females) is high but gradually falls to a more or less steady value of between

<sup>1</sup> "In countries where the social care of the insane is not adequately carried out, only a fraction of the psychotic patients enjoy medical attendance, but it is highly improbable that general paresis will be missing amongst these few, all the more so as their symptoms are usually very disturbing. If accordingly I experienced that, in a hospital containing several hundred native patients, not one case of general paresis could be found by excellently trained medical officers, we must infer that the disorder cannot in any way be as common in those parts as it is at home" (Kraepelin, 1926).

A more recent example of the "legend" theory is provided by two studies made in Bosnia and Herzegovina. In 1888, Gluck and others had reported that although syphilis was widespread in these "remote provinces", only 0.65 per cent. of native-born syphilitics developed dementia paralytica, compared with 9 per cent. of the foreign-born (Kraepelin, 1927, p. 1149). The investigation was repeated by Kojog (1939) who found that the proportion of paresis to syphilitics was the same as in Europe (5-10 per cent.). Kojog drew the conclusion that Gluck's work was entirely inaccurate; but the different findings might alternatively reflect the fact that the first world war and the general development of communication had made this part of Yugoslavia a much less remote place.

four and two to one. This is the pattern which would be expected on the hypothesis of the spread of a neurotropic strain of spirochaete. On this hypothesis, the strain would tend to reach a new country by the agency of travellers and seamen; from these men the infection would pass principally to prostitutes in the coastal towns and from them to native males. As the number of male clients is in general much higher than the number of prostitutes, the disease would at first show a preponderance of males and would only gradually spread to other females. In time, however, a balance would be reached and thereafter the sex ratio of dementia paralytica would tend to be more stable. The rapidity with which a steady ratio is reached seems to have varied markedly from country to country, and this could possibly be explained by variations in cultural attitudes to sexual behaviour. I will quote figures to indicate the early rarity and later increasing proportion of female cases in different countries.

In Paris, the sex ratio was never very high and seems to have fallen to a low level in a short time. Bayle (1826, p. 568), at the Charenton Hospital, found the ratio of males to females eight to one during the years 1816 to 1823; at the same hospital from 1823 to 1826 Calmeil (1826, p. 370), as the result of a "scrupulous examination", found the ratio to be three to one; a decade later, Foville found it 2.3 to one (Griesinger, 1861, p. 400). In 1886 (p. 245), Mickle quotes the proportion in France as 2.5 to one and a similar figure is given by Idanoff (1894). In Germany, Neumann (1859) believed that women were "very seldom" the victims of dementia paralytica. Other early writers put the ratio in Germany as 10 to one (Griesinger, 1861, p. 400); Sander (1870) found this ratio at the Charité Hospital, Berlin. In 1877, Krafft-Ebing put the figure at eight to one but twenty years later (1894) concluded that the proportion of females had considerably increased. By 1913, Kraepelin (p. 142) could say that "the relative number of women is certainly increasing in Germany" and that whereas the sex ratio had been seven or eight to one in earlier decades it had fallen to between five and two to one. In the St. Hans Hospital, Copenhagen, Heiberg's figures for paretic deaths during the years 1876 to 1890 show a gradually increasing proportion of females from 12 per cent. to 30 per cent.; from then on (to 1930) this proportion remains almost constant. Smith (1926) has given figures for the annual admission of paretics to the Kommune Hospital, Copenhagen, from 1876 to 1925; the numbers in quinquennial periods are shown in Table I, and from this it is evident that the relative proportion of male cases was at first very high but after the end of the nineteenth century remained steady at about 2.5 males to one female.

In England, the sex ratio of deaths seems to have been fairly steady at about four to one for most of the nineteenth century. In the earliest reference to the subject which I can find, however, Prichard (1835, p. 110) records that of the 16 cases seen at the Gloucester asylum since 1828 only one was female. Conolly (1849) says that at Hanwell Asylum during the decade 1839 to 1849 there were 146 male and 33 female deaths from general paralysis, adding that "in private practice I have never yet met with a case of general paralysis in a woman". Similar figures for provincial asylums are given by Wilson (1857) and Boyd (1865). From 1876 the Annual Reports of the Commissioners in Lunacy give statistics for general paralysis of the insane in England and Wales; these indicate a relatively constant sex ratio of about four to one until the second decade of the twentieth century when there is a slight increase; from 1925 there is a progressive decrease until by 1945 the ratio is 2.3 to one. These recent trends are reflected in the Registrar General's reports (Fig. 1). Discussing his earlier experiences of dementia paralytica in Scotland, Browne



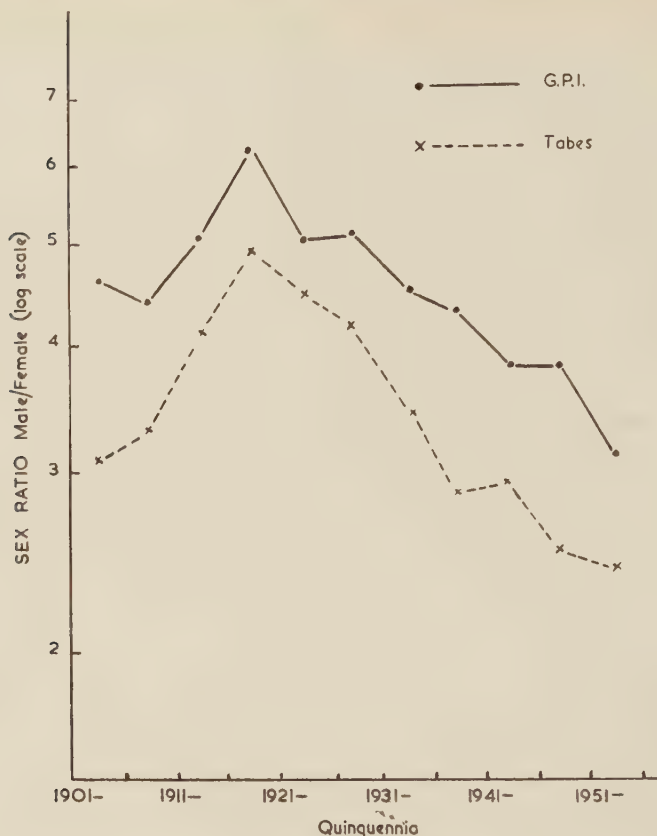


FIG. 1.—Sex ratio, by quinquennia, of deaths from General Paralysis of the Insane and from Tabes (from the Registrar General's Annual Reports for England and Wales).

(1875) said he had never been able to convince himself of the presence of the disease in the female, and Skae (1860) said that at the Royal Edinburgh Asylum he had “very seldom more than one female paralytic under my care at any one time” but rarely fewer than 22 to 25 male cases. From the Annual Reports of the General Board of Commissioners in Lunacy for Scotland, however, we learn that the male-to-female ratio of deaths was soon in the region of four to one and continued at this level into the early part of the twentieth century.

The same picture of dementia paralytica being at first rare in females and later much more common seems evident in North America. Between 1841 and 1843, Luther Bell (quoted by MacDonald, 1877) found 16 cases of the disease at Boston, but only one of these was female. Workman (1858) wrote: “In five years I have not in the Toronto Asylum met with a single case of general paralysis in a female . . . Why is it that in America general paralysis of the insane is almost if not entirely confined to males and why in Europe is there so considerable a number of exceptions to this rule?” Twenty years later (1878), Workman wrote on the subject again: during the period 1865 to 1877 he had had 95 cases of general paresis at Toronto, of whom only eight were female; and in the New York State Lunatic Asylum at Utica, where “the records are perfectly reliable”, the sex ratio of parietic deaths from 1849 to 1877 was

16 to one and in New York itself the ratio was between 15 and 20 to one. "Why a New York city asylum should show a lower proportion than an English asylum, I fail to understand." MacDonald's opinion (1877) on the gradual increase in the proportion of female cases has already been noted and his figures suggest a higher sex ratio in the Western than in the Eastern States. Figures for various asylums in the United States during the latter decades of the nineteenth century show a ratio of about eight to one (Wagner, 1902) and Berkley (1900, p. 171) makes the observation that the sex ratio had decreased during the past ten to fifteen years from nine or ten down to seven or eight. The ratio continued to decrease. Dayton's figures (1940, p. 468) show that in Massachusetts mental hospitals between 1917 and 1933, the male-to-female ratio was about four to one. In New York State hospitals between 1932 and 1941 this ratio decreased progressively from four down to three (Arieti, 1945), and figures of the U.S. Bureau of the Census (quoted by Iskrant, 1945) show the ratio for paretics in all mental institutions in 1940 was three to one.

The commonest—indeed the only—general explanation put forward to account for the increasing proportion of female paralytics in any one locality and their varying proportion in different countries was that the statistics were misleading. Thus Austin (1859, p. 59) thought the disparity had been "overstated"; Mickle (1886, p. 245) asserted that, as the relative proportion of male to female cases in England was four to one, Krafft-Ebing's earlier estimate of an eight-to-one rate was "inaccurate"; and the anonymous reviewer in the *Journal of Mental Science* (1907) believed that the increasing proportion of females was due to the fact that in this sex "the disease is now diagnosed with greater accuracy". However, we should note that although dementia paralytica may have been less dramatic in females than in males, it was not therefore less well diagnosed, for in both sexes the simple dementing type and the depressed type had been clearly described by Calmeil in 1826 and the hypochondriacal type by Baillarger in 1857. Again, if the clinical diagnosis in the female was more difficult and less often made, we should expect to find that when objective methods of diagnosis were developed early in the present century the proportion of female cases would appear to increase, but in England, at any rate, the opposite occurred, as is shown by the reports of the Board of Control and the Registrar General. The change in sex ratio of dementia paralytica during the early twentieth century is unlikely to reflect any change in diagnostic habit, as a very similar change occurred at the same time in tabes (Fig. 1).

#### CHANGES IN TYPE AND PREVALENCE

When a population is exposed to infection by a new virulent organism, the resulting disease tends in the course of years to undergo an evolution from forms which are acute and severe towards those which are milder and more chronic. This seems to have happened, for example, in the great fifteenth century epidemic of syphilis. If some such evolution can be shown to have occurred in dementia paralytica since its definite recognition 140 years ago, this may be taken to support the hypothesis that it was at that time a new disease. I will briefly consider evidence for supposing that there has been a gradual change in the proportion of clinical types of dementia paralytica and, more recently, a natural decline in its prevalence.

Both Bayle and Calmeil recognized that in its early stages dementia paralytica could be characterized either by grandiose delusions or by depression or by simple dementia, but neither of them had any doubt that of these three



types the grandiose was much the commonest. Thus Bayle (1826, p. 547) says that although not every case shows monomania yet "exceptions are very rare and are probably due to the fact that detailed observation was lacking during the first two stages of the disease". Calmeil (1826, p. 325 ff.) considered that ideas of grandeur were present in "a very great number" of insane paralytics and that simple dementia and depression (or *lypémanie* as he then called it, following Esquirol's classification) were rare. Falret, in his *Recherches sur la Folie Paralytique* (1853, p. 29), still stated that expansive delusions were the commonest mode of onset of the disease. During the second half of the century, however, changes in the relative proportion of the types began to be observed. In 1859 Calmeil published his second major work on dementia paralytica, the *Traité des Maladies Inflammatoires du Cerveau*; here (Vol. I, p. 276) he states that the depressive type had become more common during the past twelve years until now it was almost as common as the expansive type. According to Westphal (1868) "it is now established beyond contradiction that ideas of the most varied, yea even opposite description, frequently exist during the whole course of the disease or only for a certain period of it", and he adds that Bayle's belief in the overwhelming preponderance of the grandiose type "must be considered as completely refuted". Krafft-Ebing, in his monograph of 1894 (p. 25) observes that "comparison between past and present is misleading because for several decades the nature of general paralysis has been changing and in place of the classical, dramatic, obstreperous type we see more and more of the simple, dementing type". Of the various German and Austrian figures quoted by Kraepelin (1913), none puts the proportion of the expansive type as higher than 30 per cent.; the percentages of the depressive type range from 10 to 20, and of the demented type from 40 to 60.

The same gradual changes are apparent in Great Britain, though the classical type seems to have remained common for a longer time than on the continent. Thus Conolly (1849) says, "The disease is so generally associated with ideas of wealth and grandeur that when these prevail strongly in any patient we expect the paralysis to supervene. It is scarcely ever combined with melancholia." The low proportion (45 per cent.) of the grandiose type found by Austin (1859, p. 59) is perhaps to be explained by the unusually large number of females (nearly one-third) among his 135 cases<sup>1</sup>, for as late as 1871 Blandford, lecturer in psychological medicine at St. George's Hospital, still taught that "almost all, certainly nineteen out of twenty, paralytics are full of ideas of their greatness, importance and riches" (p. 260). Bullen (1893), from observations at the Wakefield Asylum, Yorkshire, between 1880 and 1890, concluded that the grandiose type was diminishing and the depressed and simple dementing types increasing in frequency (the proportion among his cases over a decade being 64 per cent., 13 per cent. and 21 per cent. respectively); he also quotes Claye Shaw as saying, "I have no doubt that we get more cases of the demented and paralysed form than we used to, and that the percentage of these is not only greater, *quoad* other forms of insanity, than formerly, but that amongst general paralytic cases it is the most common form." A later study at the Wakefield Asylum by Baird (1905) for the years 1896 to 1902 showed the proportion of grandiose cases to have fallen to 46 per cent., with corresponding increases in other types, principally the melancholic. Clouston of Edinburgh, in the sixth edition of his textbook (1904, p. 342) says of the

<sup>1</sup> All authorities have agreed that grandiose delusions were less common in female paralytics. According to Stoddart (1921, p. 433) this peculiarity was ascribed by Krafft-Ebing and Regis to the relative poverty of ideation in women.

simple dementing type, "about one-third of all the cases of the disease that I used to see were of this character, and nearly all the older medical officers of asylums say that this type is increasing while the classical grandiose type is diminishing in frequency". In a study at Brentwood Mental Hospital, Power (1930) found that between 1907 and 1922 there was a slight decrease in the number of grandiose cases, from 43 to 40 per cent. and an increase in the demented type from 30 to 50 per cent. Stoddart (1921) makes the generalization that the depressed form "is almost as frequent as, if not at present more frequent than, the expansive form".

More recent continental work indicates a continued decrease in the proportion of the classical grandiose type, though a newly distinguished type—"euphoric dementia"—appears. Thus Bostroem (1930), in 1,218 cases studied at Munich between 1920 and 1930, found the grandiose type in 10 per cent., euphoric dementia in 30 per cent., simple dementia in 34 per cent. and the depressed type in only 7 per cent. Among 680 paretics admitted to the St. Hans Hospital, Copenhagen, between 1922 and 1935, Lomholt (1944) found 14 per cent. expansive or grandiose, 2 per cent. depressive, but 60 per cent. with fatuous, euphoric dementia. Froshang and Ytrehus, studying paretics admitted to hospitals in Oslo between 1915 and 1954, found that the proportion of the classical type gradually decreased from 10 to 4 per cent.

Although a distinction between the various types of dementia paralytica is not always easy to make (especially as, during the course of the illness, the clinical picture may fluctuate) yet it seems reasonable to detect certain major changes during the past 140 years. The grandiose type, from being much the most common, has gradually become uncommon and indeed rare. The depressive type, originally rare, became more common during the latter half of the nineteenth century (between 20 and 50 per cent. of cases) but has again become rare. That there have been changes in the relative proportion of types, few if any authorities have seriously questioned. The changes cannot be accounted for merely by changes in the sex ratio, for in England they occur during a period when the sex ratio was constant; nor can they be held due to changes in prevalence of the disease, for the decline in proportion of the grandiose type continued when the prevalence was increasing during the nineteenth century and when it was decreasing during the twentieth.

There is some evidence that this decline in prevalence of dementia paralytica in the present century cannot, in England at least, be altogether or even principally ascribed to the effects of medical intervention. Figure 2 shows the mortality in England and Wales from dementia paralytica, tabes and aortic aneurysm since 1901 (the first year for which the Registrar General's reports list general paralysis of the insane and tabes separately). In 1940, the Registrar General adopted the Fifth Revision of the International List for the classification of causes of death (in which "aneurysm of the aorta" replaced the previous comprehensive category of "aneurysm") and also in the same year changed the method of selecting the assigned cause from the death certificate ("the choice now being in the main that inferred from the statement of the certificate instead of being determined by arbitrary rules of precedence"). In 1950, the Sixth Revision of the International List was adopted, by which "aneurysm of the aorta" excluded both dissecting aneurysm and aneurysm specified as non-syphilitic. These changes in method of classification account for the breaks in the curves of Figure 2. They are of little consequence for the mortality from dementia paralytica and tabes; but they imply that the figures for aortic aneurysm must, in the earlier years, have included many deaths from



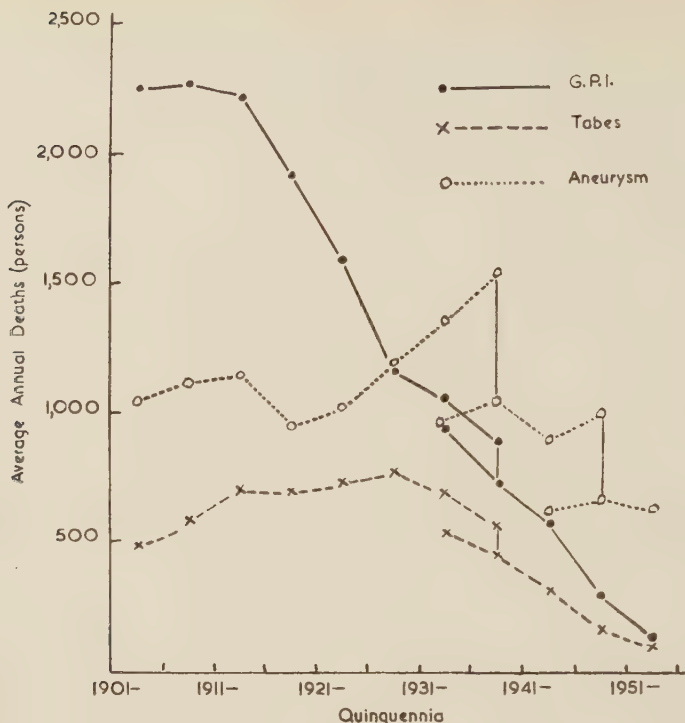


FIG. 2.—Average Annual Deaths, by quinquennia, from General Paralysis of the Insane, Tabes and “Aneurysm” (from the Registrar General’s Annual Reports for England and Wales). The breaks in the curves are explained in the text.

non-syphilitic aneurysms, so that the real decline (if any) in mortality from syphilitic aneurysm must be less than that represented by the curve (indeed, for females, the Registrar General’s actual figures of average mortality from 1946 to 1955 are higher than those from 1901 to 1910). This comparatively slight decline (or perhaps rise) in mortality from aortic aneurysm is in accordance with the figures quoted by King (1958) that the number of cases of syphilis of more than a year’s duration showed no appreciable decline between 1931 and 1952. The decline in mortality from dementia paralytica and tabes cannot, therefore, be attributed to the prevention or early treatment of syphilis. Yet the decline in mortality from tabes cannot be attributed to any specific treatment, for until penicillin was introduced after 1945 no specific treatment was known<sup>1</sup>; this decline has probably, therefore, been a natural one. From the close similarity between tabes and dementia paralytica we might argue that the decline in mortality from dementia paralytica has also been a natural one. Even if we disallow this argument, the decline is far greater than could be attributed to the effects of malarial treatment. Thus Nicole (1943) found that of 401 paretics receiving malaria only 32 per cent. were finally discharged from hospital and the same proportion is mentioned by Hutton (1941) and, from the U.S.A., by Iskrent (1945). Even if none of the discharged cases was recorded as dying from dementia paralytica, this would only lead to a mortality reduced from pre-malarial days by a factor of 1.5 whereas the mortality has in fact

<sup>1</sup> Walshe (1947, p. 174) says that he “cannot claim ever to have been satisfied that anti-syphilitic treatment influences the course of tabes”.

been reduced by a factor of 18. There remains a further possibility. The paretics who remained in hospital after treatment and who died perhaps years later of intercurrent disease may not all have been recorded as dying from dementia paralytica. If the proportion of such cases was sufficiently high, this could account for the reduction in mortality. Yet it would not explain the fall in mortality that occurred before malaria therapy was introduced, nor would it explain the continued fall in mortality after the therapy had become established. Moreover, no explanation of reduced mortality in terms of treatment would account for the very general experience that the morbidity has been declining for many years and that nowadays a case of dementia paralytica is almost a rarity. I am informed by the Board of Control that the numbers of admissions (including re-admissions) of general paralysis of the insane to mental hospitals in England and Wales fell from 1,246 in 1930 to 408 in 1950.

### CONCLUSION

Sir Humphrey Rolleston (1927) observed that many diseases have undergone modifications in form, in severity and in prevalence during historical times. Such modifications may be ascribed either to changes in the habits or constitution of the host, or to changes in an infecting organism. The disappearance of chlorosis, for example, was probably related to the disappearance of the fashion for tightly-laced corsets; the diminished prevalence of urinary calculus can be attributed to changes in dietary and drinking habits. Diphtheria, on the other hand—"a disease so sharply cut that it can hardly have been overlooked until Brettonneau of Tours" (who gave the first clear description of it in 1821)—is seen by Rolleston as probably arising *de novo* from the mutation of a hitherto harmless diphtheroid. In the same way, it may be suggested that dementia paralytica may also have been a new disease arising from a mutation in the syphilitic virus towards the end of the eighteenth century. In summary, this hypothesis is based on four considerations:

1. There is evidence (not universally accepted) that the syphilitic virus underwent some change at the end of the fifteenth century and that this was responsible for the great epidemic of that time. With regard to other changes in the nature of syphilitic disease, Klotz (1926) pointed out that there are no satisfactory descriptions of aortic aneurysm until the beginning of the sixteenth century when they become common.

2. Although dementia paralytica presents (or did present, when it first became prevalent) a very striking clinical picture, yet there is no clear description of it and certainly no evidence that it was at all common until the Parisian outbreak described by Esquirol, Georget, Bayle and Calmeil.

3. The hypothesis of a mutant strain of spirochaete spreading by venereal infection from a centre somewhere in northern France would largely explain the varying times at which dementia paralytica was recognized in different countries and the variations in prevalence and sex ratio reported in these countries during the years after its first recognition.

4. There is evidence that during the past 140 years the disease has shown gradual modifications in clinical form and a recent natural decline in prevalence. These changes are comparable with the changes that took place in the clinical course of syphilis during the years that followed the fifteenth century epidemic.

The existence of a neurotropic strain of treponema must, in the absence of laboratory proof, remain only a more or less probable hypothesis. The



attempt to support this hypothesis has been my excuse for drawing attention to the history of dementia paralytica. It is a disease which, in a relatively short time, has shown marked changes in its prevalence, distribution and clinical characteristics; and whatever may be the explanation of these changes, they permit us to reflect on a theme which it is perhaps the business of medical history to emphasize—the mutability of disease.

## ACKNOWLEDGMENT

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# AN EXPERIMENTAL STUDY OF SCHIZOPHRENIC THOUGHT DISORDER\*

By

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## HISTORICAL INTRODUCTION

FOR many years, schizophrenic thought disorder has been regarded as being due to an abnormality of concept formation of some sort. However, there has not been general agreement about the nature of this abnormality. Kurt Goldstein and his followers (9, 32, 33) have argued that schizophrenics are abnormally "concrete". That is to say, they are unable to perform inductive reasoning, since they are unable to make an abstract generalization. Norman Cameron (11, 12, 13, 14, 15, 16, 17, 18, 19) on the other hand argues that in one sense at least, schizophrenic concepts are over-generalized. He believes that the concepts formed by schizophrenics are "over-inclusive". They are unable to maintain the normal conceptual boundaries, and incorporate into their concept elements (some of them personal) which are merely associated with the concept, but are not an essential part of it. This makes their thinking both over-general, and less precise than normal. A large number of studies have been carried out to test both these hypotheses.

## STUDIES OF "CONCRETENESS" OF THINKING

Bolles and Goldstein (9) first attempted to demonstrate abnormal "concreteness" of thinking by using the Goldstein-Scheerer (34) battery of tests for concept formation with a group of 16 schizophrenics. While they were reported as "concrete" according to the scoring criteria used, no control group was tested.

Rapaport *et al.* (65), using an object sorting test similar to Goldstein's, found that a group of schizophrenics were no more "concrete" than normals. However, the concepts they evolved were unusual, and the term "syncretistic" was used to describe them.

McGaughran (58, 59) and McGaughran and Moran (60) report an interesting series of studies with the Goldstein object sorting test. They scored the sorting behaviour along two dimensions. The first was called "conceptual

\* The senior author is responsible for the review of the literature, the experimental design and analysis of data, the theoretical formulation and writing up the results. Dr. Mattussek and Dr. George gave the tests during the course of a stay at the Institute of Psychiatry. Dr. Mattussek also assisted in the selection of the cases.



freedom" or "open-closed", which they identify with "concreteness". It is assessed by the number of objects the concept covers (the degree of generality). The second was called a "public-private" dimension and was a rating of the extent to which the concept formed was usual or unusual. They found that, far from being "concrete", schizophrenics formed slightly more extensive concepts than normals. Their concepts, however, tended to be "private" or unusual.

Another group of studies has made use of the Vigotsky (74) test for concept formation, which, unlike the Goldstein tests, requires the subject to form only one concept, the score being a function of the speed with which this is done. Kasanin and Hanfmann (50, 51), Hanfmann and Kasanin (38, 39) and Kasanin (49) report several studies using this test with schizophrenics. They demonstrated that the score was probably related to educational level, but that even when this is controlled, schizophrenics do worse than normals. However, these results are not unambiguous, since poor scores on this test could be purely a function of mental slowness, or a tendency to produce unusual generalizations. They do not necessarily indicate an inability to generalize. Indeed, Fisher (28), using the Vigotsky test material as a sorting test to determine how many different sortings could be achieved, found that 20 schizophrenics and 20 hysterics were not differentiated (although 20 normals who were younger and brighter than either group, did better).

Studies by Rashkis, Cushman and Landis (67) and Rashkis (66), using a rather different type of word sorting and number sorting test, produced very similar results inasmuch as schizophrenics were inferior in their performance, not because they could not generalize, but because they produced very unusual generalizations.

Feldman and Drasgow (26) developed a test of concept formation using pictures on cards. On each card were four pictures, and on each two different groupings of three objects each were possible. While schizophrenics were inferior to normals on this test, it is possible that this is because they think of unusual generalizations, and not because they are "concrete".

Thus the studies using "sorting" tests of concept formation have produced more or less consistent results. Schizophrenics cannot be regarded as "concrete" in the sense of being unable to generalize at all. Rather, they tend to produce unusual generalizations.

Another different technique for studying the ability to form concepts, consists in asking the subjects to sort a long series of cards into two groups, correcting the subject when an error is made. The principle of sorting is not explained beforehand, but must be *learned* during the course of the experiment. This technique was used by Heidebreder (41, 42, 43, 44, 45, 46, 47, 48) for the study of concept formation in normal people. The Wisconsin Sorting Test (8, 36, 37) makes use of a similar technique. During the course of the test, concepts must be learned, and several times the principle of sorting is changed, to force the subject to learn a new concept. Fey (27) used the test with a schizophrenic and a normal group, and found that the schizophrenics were inferior, possibly not because they were unable to learn the concept, but, having learned it, they had "... difficulty in holding the correct set ...".

The remaining group of studies of "concreteness" attempt to assess it by rating the quality of definitions given to words or the explanations of proverbs. The results have been consistent and these studies all report schizophrenics as being more "concrete". For example Flavell (29) gave a multiple choice vocabulary test to 24 schizophrenics and reported that they chose more

"concrete" definitions than did normals. Proverbs have been used in studies by Wegrocki (76), Benjamin (7), Becker (6) and Gorham (35). Gorham (35) reports two very large studies, one using a matched group of 100 normals and 100 schizophrenics. He used both the ordinary form of the proverbs test, and a multiple choice version. Schizophrenics consistently gave more "concrete" interpretations.

In the light of the earlier studies discussed, these consistent findings with the proverbs test cannot be regarded as unambiguous. There is no doubt that schizophrenics tend to define words and interpret proverbs peculiarly. However this is not necessarily due to an inability to generalize. It is possible that unusual generalizations given in response to proverbs are often labelled "concrete". It is also conceivable that, just as they tend to use and define words peculiarly, some schizophrenics may interpret words they hear unusually. Some, for example, may interpret the instructions of the proverbs test as allowing either a general statement of the principle illustrated *or* the use of an apt concrete illustration of the meaning it has for them. These studies have apparently not established what generalizations these schizophrenics might have produced, had they been encouraged to continue talking long enough.

It is perhaps not unfair to conclude that the studies of "concreteness" so far carried out, have not succeeded in demonstrating that schizophrenics are unable to make abstract generalizations, although there is ample evidence that the generalizations they do make tend to be unusual.

#### STUDIES OF "OVER-INCLUSIVE" CONCEPT FORMATION

Norman Cameron (11, 12, 13, 14, 15, 16, 19) was one of the first to explain much of the thought disorder in schizophrenia in terms of over-inclusive concept formation, although Schilder (70) and Bychowski (10) among others have described a similar type of thinking disturbance. More recently Angyal (1) and Lovibond (56) have reformulated this theory.

Cameron first used the theory to account for the performance of small groups of deteriorated schizophrenic patients on the Vigotsky test, and on a sentence completion test. He reported that the schizophrenics were unable to preserve the "conceptual boundaries" of the task. In solving a problem the schizophrenics "... included such a variety of categories at one time that the specific problems became too extensive and too complex for a solution to be reached ...". Not only are their concepts "over-inclusive" but their thinking is disturbed by the "interpenetration of personal themes", although this might be regarded as one aspect of the general disorder of "over-inclusion".

A surprising number of studies have been conducted to investigate "over-inclusive" thinking in schizophrenia. The results consistently support the theory. Shneidman (73) developed a modification of the Thematic Apperception Test in which the subject selects from a large group of different human figures, those he believes suited to each background scene, makes up a picture, and then tells a story about it. As predicted from Cameron's theory, schizophrenics' stories were "over-inclusive" in several aspects. For example, they chose significantly more figures as relevant to each background, than did normals.

Zaslow (78) developed a simple test of over-inclusion in concept formation, which consisted of a series of 14 cards, each containing a drawing which gradually progressed from an equilateral triangle to a perfect circle. Various methods were used to determine how many cards the subjects would incorporate into the concepts "triangle" and "circle". As predicted, schizophrenics included significantly more cards than normals. However Kugelmass and



Fondeur (54) were unable to repeat these results at an acceptable level of significance, probably because of the unreliability of the test.

White (77), testing a matched schizophrenic and normal group, asked his subjects to group 15 cards with a word printed on each, in any way they liked. The schizophrenics tended to form very large, vague categories, forming concepts such as "suspicion" or "having to do with God".

Daston, King and Armitage (23) read two short stories aloud to 25 paranoid schizophrenics and 27 matched normals. Afterwards the subjects were given a check list of 36 positive and 36 negative statements about the characters in the stories. The schizophrenic group checked off significantly more adjectives than the normals.

Moran (61) tested several deductions from Cameron's theory with a group of 40 schizophrenics and 40 matched normals. The subjects were first given 25 words to define. There were no differences in the "conceptual level" of the definitions given, thus not supporting the hypothesis that schizophrenics are "concrete". The subjects were then asked to give as many synonyms as possible for each word. As predicted, the schizophrenics' synonyms were less precise. When asked to free associate to the words, the schizophrenics produced more "distant" associations. When asked to incorporate the words into a sentence, their sentences were unclear, contradictory and ungrammatical. The subjects were also given a test in which each word (printed on a page) was followed by 8 response words, including neologisms. They were asked to underline each word which they regarded as an essential part of the concept denoted by the stimulus word. As predicted, the schizophrenics did not underline significantly fewer correct words, but did underline significantly more of the distantly related words. Epstein (24) developed a very similar test, and obtained the same results with a schizophrenic and a normal group.

Lovibond (56) using the Goldstein Object Sorting test, with schizophrenics and normals, employed a rating system to assess the amount of "over-inclusion" in sorting behaviour. Schizophrenics were rated as more over-inclusive.

Chapman (21) and Chapman and Taylor (22) report a series of interesting experiments which have also confirmed the theory of over-inclusion. They made use of card sorting tests of different types, and found that, when asked to sort according to a specific concept (e.g. "fruit"), schizophrenics tended to include in this category similar cards (e.g. cards with the names of vegetables), but not completely dissimilar cards. Normals did not do this. In another experiment, they presented the subjects with cards containing four pictures, some of which illustrated a concept. The subjects were asked to sort the cards according to a concept, but to disregard all the pictures on the cards except the picture in the lower right hand corner. As predicted, the schizophrenics were influenced by the irrelevant "distractor" items, whereas the normals were not. There was no evidence of "concreteness", or inability to sort at all, since the number of errors made varied directly with the number of distractor items, there being no significant difference between normals and schizophrenics when these distractor items were not present.

It must be concluded from these studies that Cameron's theory of over-inclusion has received strong support from the experiments so far performed.

#### THEORETICAL FORMULATION

It is possible to reformulate Cameron's theory of over-inclusion in a slightly more general way so that a number of predictions follow from it.

Concept formation can be regarded as largely the result of discrimination learning. When a child first hears a word in a certain context, the word is associated with the entire situation (stimulus compound). As the word is heard again and again, only certain aspects of the stimulus compound are reinforced. Gradually the extraneous elements cease to evoke the response (the word), having become "inhibited" through lack of "reinforcement". This "inhibition" is in some sense an active process, as it suppresses a response which was formerly evoked by the stimulus. "Over-inclusive thinking" may be the result of a disorder of the process whereby "inhibition" is built up to "circumscribe" and "define" the learned response (the word or "concept"). In short, it could be an extreme degree of "stimulus generalization".

The same theory can be expressed in different terms. All purposeful behaviour depends for its success on the fact that some stimuli are "attended to" and some other stimuli are ignored. It is a well-known fact that when concentrating on one task, normal people are quite unaware of most stimuli irrelevant to the task. It is as if some "filter mechanism" cuts out or inhibits the stimuli, both internal and external, which are irrelevant to the task in hand, to allow the most efficient "processing" of incoming information. Over-inclusive thinking might be only one aspect of a general breakdown of this "filter mechanism".

It was the purpose of the present series of experiments, to test a fairly large number of predictions from this general theory, on a small group of schizophrenic patients, using a group of neurotic patients as controls.

#### THE EXPERIMENTAL SUBJECTS

All the subjects tested were in-patients of the Maudsley Hospital.

The experimental group consisted of 18 schizophrenic patients, 12 males and 6 females. These were selected as being typical of this diagnostic category by the psychiatrist in charge of the case. They were seen independently by a second psychiatrist (Dr. Mattussek) who rejected any doubtful cases. Six were labelled "paranoid schizophrenia", one was labelled "paraphrenic schizophrenia", one "acute schizophrenia", one "simple schizophrenia" and the remainder were merely labelled "schizophrenia". None of the patients were regarded as chronic, although many had had previous admissions with the same illness. Needless to say, all were sufficiently well to co-operate in the rather lengthy and exacting testing programme involved.

The control group consisted of 16 neurotic patients, 7 males and 9 females. These patients were selected from the in-patient neurotic population in the same way. Neurotics thought to have some psychotic features were rejected. The diagnoses which had been given them were as follows: reactive depression 4; anxiety state 6; obsessional neurosis 2; anxiety hysteria 1; hysteria 1; psychogenic eczema 1; immature personality 1. Neurotic patients were used as a control group as they are not thought to suffer from thought disorder, and the factor of length of hospitalization was thus roughly controlled.

Table I compares the groups with respect to age and general intelligence.

It can be seen that the two groups are fairly well matched on all these variables. It is surprising that, while the schizophrenics are a trifle duller than the neurotics on the Mill Hill Vocabulary test (68) they are a trifle brighter on the Nufferno Level Test (31), a "speed free" non-verbal test of "general intelligence". This is not consistent with the findings usually reported, that schizophrenics show a "vocabulary-G" discrepancy consistent with some



TABLE I  
*Age and General Intellectual Status of the Two Groups*

|                                       |                               | Schizophrenics<br>(N=18)         | Neurotics<br>(N=16) |
|---------------------------------------|-------------------------------|----------------------------------|---------------------|
| Age                                   | Mean .. .. .                  | 28·83                            | 31·69               |
|                                       | Standard deviation .. ..      | 8·37                             | 9·53                |
|                                       | Range .. .. .                 | 21-47                            | 18-48               |
|                                       | Significance of difference .. | Not significant ( $t=0\cdot30$ ) |                     |
| Mill Hill<br>Vocabulary<br>raw scores | Mean .. .. .                  | 56·58                            | 58·36               |
|                                       | Standard deviation .. ..      | 9·42                             | 9·76                |
|                                       | Range .. .. .                 | 36-71                            | 41-73               |
|                                       | Significance of difference .. | Not significant ( $t=0\cdot47$ ) |                     |
| Matrices<br>raw scores                | Mean .. .. .                  | 42·43                            | 46·07               |
|                                       | Standard deviation .. ..      | 9·60                             | 11·32               |
|                                       | Range .. .. .                 | 22-53                            | 10-57               |
|                                       | Significance of difference .. | Not significant ( $t=0\cdot91$ ) |                     |
| Nufferno<br>Level Test<br>raw scores  | Mean .. .. .                  | 315·12                           | 308·66              |
|                                       | Standard deviation .. ..      | 165·22                           | 140·54              |
|                                       | Range .. .. .                 | 100-633                          | 133-533             |
|                                       | Significance of difference .. | Not significant ( $t=0\cdot11$ ) |                     |

measure of general deterioration. It must be pointed out however, that the schizophrenics in the present study cannot be regarded as chronic cases, and on clinical grounds were not judged to have deteriorated.

The two groups were also fairly well matched for educational attainment. Six of the 16 neurotics had attended grammar school, while 7 of the 18 schizophrenics had attended grammar school. The remaining subjects had received elementary only, or elementary and/or "secondary modern" education.

#### INVESTIGATION OF INTELLECTUAL SPEED

It is a fairly well established finding that schizophrenics are unusually slow at problem solving (2, 3, 4, 20, 40, 52, 62, 71, 72). Several of these studies (40, 62, 72) have made use of the Nufferno Speed Tests (30). These tests consist of Thurstone type letter series items, and the solution speed for each individual item is obtained separately, the incorrect answers being excluded. It seems possible that "over-inclusion" may be the fundamental cause of intellectual slowness in schizophrenia. Normal people, when solving a letter series problem, consider only a limited range of possible solutions. Indeed, they regard only the sequence of the letters as being relevant to the task. It is possible that schizophrenics do not exclude other aspects of the letter series items in considering possible solutions. For example they might also take into account their associations to the letters. This, in itself, would not necessarily produce an incorrect answer, since any answer, whatever aspect of the material it is based on, must explain the letter series given in the question. Solutions based on irrelevant aspects of the material might be considered by schizophrenics, but rejected if they did not "fit". In short, it is possible that schizophrenics are slower on letter series items merely because for them, the difficulty level is increased, there being more items of information to take into account. In other words, over-inclusion would lead to a larger pool of possible (but incorrect) solutions to be considered for each item. This would not necessarily lead to an increase in the number of errors made, since they might be recognized as wrong.

It would however produce on the *average* a slower solution time per item. It should *also* lead to increased variability of solution times.

If this were the case, slowness could not be regarded as a fundamental disorder in schizophrenia (as Babcock regarded it) but rather as a secondary disorder. It was predicted therefore, that tests of intellectual slowness would discriminate between the groups less well than direct measures of "over-inclusion".

Three forms of the Nufferno speed tests (30) were used in the present study. Test A1 consists of a group of easy items of homogeneous difficulty level. It was given individually under "unstressed" conditions. That is, the subjects were told to work at their own rate, and they were unaware that they were being timed. Test A2 is identical to test A1, and is of the same level of difficulty. However it was given under "stressed" conditions. That is to say, the subjects were told to work as quickly as possible, and were aware that they were being timed. (The "individual" method of giving the test was still used.) Test B1 is similar to the other tests, but consists of a homogeneous set of more difficult items. It was also given individually under "stressed" conditions. The scores obtained are "mean log time" scores (i.e. the average of the logarithm of the solution time for each item solved correctly). The results are presented in Table II.

TABLE II  
*Nufferno Speed Test Scores for the Two Groups*

|            |                               | Schizophrenics                                                 | Neurotics     |
|------------|-------------------------------|----------------------------------------------------------------|---------------|
| Speed test | Mean .. .. .                  | 1.0991                                                         | 1.0584        |
| A1         | Standard deviation .. ..      | 0.1608                                                         | 0.1748        |
| Individual | Range .. .. .                 | 0.7805-1.4881                                                  | 0.8200-1.4600 |
| unstressed | Significance of difference .. | Not significant ( $t=0.63$ )                                   |               |
| Speed test | Mean .. .. .                  | 1.0545                                                         | 0.9197        |
| A2         | Standard deviation .. ..      | 0.2529                                                         | 0.1412        |
| Individual | Range .. .. .                 | 0.6238-1.5885                                                  | 0.6442-1.1119 |
| stressed   | Significance of difference .. | Significant at 5 per cent. level<br>(1 tail test) ( $t=1.70$ ) |               |
| Speed test | Mean .. .. .                  | 1.2851                                                         | 1.2000        |
| B1         | Standard deviation .. ..      | 0.2501                                                         | 0.2297        |
| Individual | Range .. .. .                 | 0.8834-1.6755                                                  | 0.7643-1.6692 |
| stressed   | Significance of difference .. | Not significant ( $t=0.93$ )                                   |               |

These results are consistent with previous findings in that the schizophrenics are slower than the neurotics on each test. However the mean differences achieve statistical significance for only one test (A2), and then only at the 5 per cent. level by a "one-tail" test. As will be seen later, direct measures of over-inclusion differentiate the groups at a very high level of significance, so that the prediction that tests of intellectual speed will differentiate the groups less well, is substantiated.

While intellectual speed tests themselves do not differentiate well, it is possible that some measure of the individual's slowness relative to his general intellectual level might differentiate better. In order to examine this possibility, "speed-level" discrepancy scores were calculated for all the subjects. This score was obtained by converting each subject's level score into a standard score on the basis of Furneaux's published norms. The speed score obtained on test B1 was also transformed into a standard score. (In this calculation, the signs were



reversed, so that a high speed standard score represents a fast performance.) The discrepancy score is merely the level standard score minus the speed standard score, plus 5.000. This constant was added to eliminate negative numbers (subjects whose speed scores were better than their level scores). The results are presented in Table III.

TABLE III  
*Speed-Level Discrepancy Scores for the Two Groups*

|                                     |                               | Schizophrenics               | Neurotics   |
|-------------------------------------|-------------------------------|------------------------------|-------------|
| Speed-level<br>discrepancy<br>score | Mean .. .. .                  | 5.3710                       | 4.7694      |
|                                     | Standard deviation .. ..      | 2.1214                       | 1.9230      |
|                                     | Range .. .. .                 | 1.307-8.193                  | 0.530-7.726 |
|                                     | Significance of difference .. | Not significant ( $t=0.93$ ) |             |

This table suggests that, on the average, the schizophrenics obtain a level score 0.37 standard deviations higher than their speed score (in terms of Furneaux's norms). They are therefore rather slow in comparison with the level they attain. The neurotics on the other hand are slightly quicker than their level score would suggest, since on the average their speed score is 0.23 standard deviations higher (i.e. better) than their level score. Due to the wide variability however, the difference between the groups is not statistically significant. In fact the speed scores differentiate just as well as the discrepancy score.

If schizophrenics tend to be somewhat slow intellectually, it is possible that they tend to compensate for this by working at their maximum rate most of the time. Thus, when asked to speed up and work as quickly as possible, very little change should occur. The *stress gain* score, was used as a measure of the extent to which the subjects were able to speed up when asked to. This is merely the mean log time for test A1 (given "unstressed") minus the mean log time for test A2 (given "stressed"). A constant of 0.200 was added to eliminate negative scores. Table IV gives the results obtained.

TABLE IV  
*"Stress-Gain" Scores for the Two Groups*

|                                  | Schizophrenics                                                 | Neurotics     |
|----------------------------------|----------------------------------------------------------------|---------------|
| Mean .. .. .                     | 0.2668                                                         | 0.3386        |
| Standard deviation .. ..         | 0.1463                                                         | 0.1292        |
| Range .. .. .                    | 0.0064-0.6262                                                  | 0.1789-0.5481 |
| Significance of difference .. .. | Significant at 5 per cent. level (1 tail test)<br>( $t=1.70$ ) |               |

The differences are in the expected direction. Neurotics are able to speed up to a greater extent than schizophrenics when asked to work as quickly as possible. However the differences are small, attaining the 5 per cent. level of significance only on a "one tail" test.

If schizophrenics are slow thinkers, it is possible that they might compensate for this by a greater degree of persistence. Indeed, Furneaux (31) has shown that scores on the level test are a function of speed, "error" and persistence. Two attempts were made to assess the persistence of the subjects on intellectual tasks. Both were unsatisfactory. The subjects were first given an insoluble but simple-looking intellectual task. Unfortunately, in spite of warnings not to do so, the patients discussed it among themselves on the wards, arriving at the joint conclusion that the task was insoluble. This experiment was thus abandoned. The second measure used was the sum of the two longest

times (in seconds) spent during the level test on items which were subsequently abandoned or solved incorrectly. Since this measure was only introduced after the first had failed, measurements were not obtained for all the subjects. The results obtained are given in Table V.

TABLE V  
*Persistence Scores for the Groups*

|                            | Schizophrenics (N=10)        | Neurotics (N=8) |
|----------------------------|------------------------------|-----------------|
| Mean                       | 137.40                       | 132.38          |
| Standard deviation         | 89.09                        | 71.94           |
| Range                      | 32-303                       | 72-273          |
| Significance of difference | Not significant ( $t=0.13$ ) |                 |

These results are in the expected direction, but not significant statistically.

#### SUMMARY AND CONCLUSIONS OF EXPERIMENTS ON INTELLECTUAL SPEED

The results suggest that slowness of problem solving is not an important intellectual defect in schizophrenia. This is not consistent with Babcock's hypothesis that intellectual slowness is of fundamental importance in schizophrenic thought disorder. The findings are consistent with the hypothesis that slowness of problem solving in schizophrenia is a by-product of the more fundamental disorder of "over-inclusive" thinking.

#### INVESTIGATION OF MOTOR SPEED

A number of previous studies (2, 3, 5, 72) have found schizophrenics to be unusually slow at extremely simple psychomotor tasks, such as the speed of writing from dictation, or even the speed of writing one's own name. It is difficult to see how this type of slowness can be explained in terms of "over-inclusive" thinking, since these tasks would seem to require very little thought indeed.

In order to see whether these findings characterized the present group, four subtests from the Babcock-Levy test (5) were used. These were:

1. The speed of writing "the United States of America". The score was merely the number of seconds required.
2. The speed of writing one's own name. The score was the number of seconds required.
3. The speed of writing a simple sentence from dictation. The sentence used, from Babcock's battery (item 12 mc) was "I hope to leave here very soon".
4. The Babcock-Levy "substitution" test (test 7 in Babcock's battery) was the final item. This test merely requires the subject to write the appropriate number (from 1 to 5) in a symbol, using a key provided. The test would appear to be a function of simple perceptual and motor speed, although some rote learning is probably also involved. Babcock's scores were not followed. The score used in the present study was merely the average time in seconds required to complete each line of the test, there being five lines in all.



The results obtained are given in Table VI.

TABLE VI  
*Simple Psycho-Motor Speed Test Scores for the Two Groups*

|                                |                            | Schizophrenics               | Neurotics |
|--------------------------------|----------------------------|------------------------------|-----------|
| Speed of writing U.S.A.        | Mean .. .. .               | 13.95                        | 11.08     |
|                                | Standard deviation ..      | 10.53                        | 2.73      |
|                                | Range .. .. .              | 7.5-51.0                     | 6.5-15.0  |
|                                | Significance of difference | Not significant ( $t=0.92$ ) |           |
| Speed of writing own name      | Mean .. .. .               | 10.47                        | 8.08      |
|                                | Standard deviation ..      | 4.56                         | 2.88      |
|                                | Range .. .. .              | 5.5-24                       | 4.5-14    |
|                                | Significance of difference | Not significant ( $t=1.65$ ) |           |
| Speed of writing a sentence    | Mean .. .. .               | 13.27                        | 11.00     |
|                                | Standard deviation ..      | 6.63                         | 2.07      |
|                                | Range .. .. .              | 8-35                         | 7.5-14    |
|                                | Significance of difference | Not significant ( $t=1.14$ ) |           |
| Babcock-Levy substitution test | Mean .. .. .               | 19.34                        | 16.41     |
|                                | Standard deviation ..      | 6.22                         | 4.29      |
|                                | Range .. .. .              | 9.2-33.2                     | 9.0-24.0  |
|                                | Significance of difference | Not significant ( $t=1.37$ ) |           |

All the mean differences are consistent, in that the schizophrenics were slightly slower. However none are large enough to reach statistical significance. These tests differentiate even less well than do the tests of intellectual speed.

#### SUMMARY AND CONCLUSIONS OF EXPERIMENT ON MOTOR SPEED

There is no evidence that psychomotor retardation is an important aspect of the psychological abnormalities of the schizophrenic patients in the present study.

#### INVESTIGATION OF "CONCREteness"

##### (a) *Results Using the Goldstein-Scheerer Tests*

Previous studies suggest that schizophrenics are "concrete" in their performance on these tests, if Goldstein and Scheerer's scoring (34) criteria are used. If the tests are scored in this way however, the result will be ambiguous. Goldstein and Scheerer do not distinguish between what might be called a "bizarre" sorting, and a failure to sort at all. Both performances are rated as "concrete". If the theory of "over-inclusion" is correct, and schizophrenics perceive more aspects of the test material as relevant to the task than do normals, they will have more data on which to base possible sortings. If they base their sorting on what normal people would regard as irrelevant aspects of the material, the sorting will be judged to be bizarre, or at least unusual. However, if the schizophrenic does not distinguish between a "bizarre" sorting and a normal "abstract" sorting, which type of response occurs first will be completely random. If Goldstein's method of administration is followed, and the initial solution is an unusual one (e.g. "patterning"), the subject's performance will be rated as "concrete". Furthermore, the subsequent test procedure will be altered, and in many cases the subject will not be allowed to continue to sort the material, and it will not be possible to determine whether or not he will later produce spontaneously an "abstract" solution.

It was therefore predicted from the theory of over-inclusion, that, if Goldstein and Scheerer's scoring system were followed, the schizophrenics would be significantly more "concrete" than the neurotics, by virtue of their "over-inclusive" tendencies. However these tests should not differentiate as well as tests specifically designed to measure "over-inclusive" thinking.

Only two tests in the Goldstein-Scheerer battery were used, the "colour-form" test, and the "object sorting test". These were administered in accordance with the instructions in the manual. Unfortunately, although the authors give a detailed description of the types of "concrete" responses to these tests, they do not give a system of scoring them. A five-point rating scale for "concreteness" was therefore used for each test. A score of 1 indicates a completely "abstract" performance, while a score of 5 indicates a completely "concrete" performance. These rating scales were very carefully constructed on the basis of the criteria laid down in the manual, and each level of performance was defined as precisely as possible. For example, rating "3" on the colour-form test was defined as follows: "Correct sorting for one principle (colour or shape), but inability to shift spontaneously. However, immediate success with the assistance of (a) the white sides turned up, if appropriate, or (b) immediate recognition and acceptance of the sorting presented by the examiner and an acceptable definition at either (a) a completely 'abstract' level, e.g. 'I have sorted for shape' or (b) a slightly 'concrete' level, e.g. 'these are all round, these all square, etc.'"

The results obtained are presented in Table VII.

TABLE VII  
*Ratings of "Concreteness" on the Goldstein-Scheerer Sorting Test*

|                        |                            |    |    | Schizophrenics                                         | Neurotics |
|------------------------|----------------------------|----|----|--------------------------------------------------------|-----------|
| Colour-Form<br>Test    | Mean                       | .. | .. | 2.57                                                   | 1.64      |
|                        | Standard deviation         | .. | .. | 1.79                                                   | 1.15      |
|                        | Range                      | .. | .. | 1-5                                                    | 1-4       |
|                        | Significance of difference |    |    | Not significant ( $t=1.64$ )                           |           |
| Object-Sorting<br>Test | Mean                       | .. | .. | 4.21                                                   | 2.79      |
|                        | Standard deviation         | .. | .. | 0.80                                                   | 1.25      |
|                        | Range                      | .. | .. | 2-5                                                    | 1-5       |
|                        | Significance of difference |    |    | Significant beyond 0.1 per cent.<br>level ( $t=3.60$ ) |           |

These results are more or less as expected. The colour-form test just fails to produce a difference significant at the 5 per cent. level (1 tail test), but is in the expected direction. On the other hand the object sorting test produces a highly significant difference (beyond the .001 level on a two tail test). This is probably because the object sorting test material, being extremely heterogeneous, provides more scope for the schizophrenics to produce "over-inclusive" or unusual sortings of the type that are sometimes labelled "concrete" when the scoring criteria are applied. (Evidence that this is the case will be presented later in connection with a similar test.)

It is of interest that, if the performance of the neurotic group is taken as a criterion, the object sorting test is more difficult than the colour-form test. Indeed, according to the rating scale used, the average neurotic performance on the object sorting test would be judged as definitely "concrete". Only two neurotic subjects gave a perfectly "abstract" performance according to Goldstein and Scheerer's criteria (i.e. getting a rating of "1"). On the other



hand, only four members of the neurotic group (and 8 members of the schizophrenic group) failed to perform perfectly on the colour-form test (i.e. getting a rating of "1").

#### (b) *Results Using Benjamin's Proverbs Test*

It has already been argued that, although schizophrenics are consistently reported as being "concrete" in their explanations of proverbs, that these findings could also be interpreted as being due to over-inclusive thinking. Benjamin's proverbs test was given to the present group, in order to demonstrate that, when scored in the traditional way, the schizophrenic group will be moderately "concrete", but that this score will not differentiate as well as a direct measure of "over-inclusive" thinking.

Benjamin's (7) list of 14 proverbs was used. Since there appears to be no standard way of administering this test, it is worth recording the precise instructions which were used in the present study. They were as follows: "I am going to read a few proverbs and what I want you to do is simply give the meaning of each one as simply as you can. Let me give you an example 'Too many cooks spoil the broth'. This means that when too many people are concerned in a task, they are likely to be less efficient than a single person would be. Now I am going to read some more proverbs and I want you to explain what they mean. Also tell me when you have finished." (The proverbs were then read one at a time and the answers recorded verbatim, no other instructions being given.)

The answer to each proverb was merely rated "abstract" or "concrete" according to Benjamin's general criteria. The score was the total number of abstract answers given. If, however, no answer at all was given, that particular proverb was not counted (e.g. some subjects claimed not to have heard of some of the proverbs, and these were excluded). When proverbs were omitted in this way, the score obtained was pro-rated so as to be a proportion of 14 (the highest possible score).

The results are given in Table VIII.

TABLE VIII  
*Number of "Abstract" Answers Given to Benjamin's Proverbs*

|                            |       | Schizophrenics               | Neurotics |
|----------------------------|-------|------------------------------|-----------|
| Mean                       | .. .. | 7.33                         | 9.43      |
| Standard deviation         | .. .. | 4.20                         | 2.79      |
| Range                      | .. .. | 0-14                         | 3-13      |
| Significance of difference | .. .. | Not significant ( $t=1.57$ ) |           |

These results are in the direction of those reported in the literature, but just fail to achieve statistical significance at the 5 per cent. level (one tail test).

#### (c) *Results Using a Concept Formation Test Modified from Feldman and Drasgow*

Feldman and Drasgow (26) devised a simple test for concept formation which they found differentiated between schizophrenics and normal subjects. The details of their test were not reported, but a test constructed on similar principles was employed in the present study.

This test of concept formation is simpler than the methods previously described. The subjects were presented with four objects drawn on a card. For example, Card 1 contains four circles. One of the circles is smaller than the

other three, but one of the large circles is coloured black. In each card it is possible to group three of the objects together for one reason, but another three of the objects can be grouped together for a different reason. For example, in Card 1, the three white circles can be grouped together, or alternatively, the three large circles can be grouped together. The test contained 20 cards. For each card the subject was asked to say which three objects could be grouped together, and why, and then to discover an alternative method of grouping another three objects together. Some of the cards contained simple geometrical designs, but most of them depicted everyday objects (e.g. a banana, an orange, a rubber ball and an apple—three are edible and three are round).

It seemed that this test would be less likely to be influenced by over-inclusive thinking than the sorting tests already discussed, as the material is less complex, and would therefore be a better measure of the ability to abstract, uncontaminated by other factors.

The test was given without a time limit, but a record was taken of the performance for each card within the first minute. Thus two scores were possible, one based on no time limit, and one on the first minute's performance. This was done because Feldman and Drasgow had given the test with a time limit of 1 minute per item, and the effect of imposing such a time limit could thus be observed.

The "total abstraction" score used in the present study was merely the total number of correctly identified concepts (the total possible score is 40 as there are two concepts per card).

The results are given in Table IX.

TABLE IX  
*"Total Abstraction" Scores for the Two Groups*

|                               |                               | Schizophrenics               | Neurotics |
|-------------------------------|-------------------------------|------------------------------|-----------|
| Within the<br>first<br>minute | Mean .. .. .                  | 30.00                        | 32.46     |
|                               | Standard deviation .. ..      | 4.91                         | 4.70      |
|                               | Range .. .. .                 | 21-38                        | 23-39     |
|                               | Significance of difference .. | Not significant ( $t=1.33$ ) |           |
| With no<br>time limit         | Mean .. .. .                  | 31.14                        | 33.15     |
|                               | Standard deviation .. ..      | 4.67                         | 4.18      |
|                               | Range .. .. .                 | 24-39                        | 25-39     |
|                               | Significance of difference .. | Not significant ( $t=1.18$ ) |           |

There is no evidence that a time limit of one minute per card has any appreciable effect on the scores of the two groups. Under neither condition is the difference significant. There is thus no evidence in the present study that schizophrenics are "concrete" on this test.

Goldstein and Scheerer (34) identify "concreteness" and "rigidity". They maintain that people who have difficulty in making an abstract generalization are rigid in that, having once produced one type of abstract classification, they have extreme difficulty in producing an alternative generalization for the same material. More evidence will be presented later that schizophrenics are not rigid in this sense. However, the present test provides a method for assessing this type of rigidity. On each card, there are two different ways of grouping the objects. Rigid people, having grouped them in one way, should find it extremely difficult to find the alternative grouping. In other words, they should have a low proportion of "double concepts" (cards in which both groups are obtained). The rigidity score used was merely the number of "double concepts"



obtained, expressed as a proportion of the "total abstraction" score. A high score suggests flexibility, a low score, rigidity. The results with and without time limit are presented in Table X.

TABLE X  
"Rigidity" Scores for the Two Groups

|                               |                               | Schizophrenics                                                 | Neurotics |
|-------------------------------|-------------------------------|----------------------------------------------------------------|-----------|
| Within the<br>first<br>minute | Mean .. .. .                  | 0.343                                                          | 0.406     |
|                               | Standard deviation .. ..      | 0.084                                                          | 0.084     |
|                               | Range .. .. .                 | 0.19-0.47                                                      | 0.24-0.50 |
|                               | Significance of difference .. | Significant at 5 per cent. level<br>(1 tail test) ( $t=1.97$ ) |           |
| With no<br>time limit         | Mean .. .. .                  | 0.364                                                          | 0.409     |
|                               | Standard deviation .. ..      | 0.071                                                          | 0.082     |
|                               | Range .. .. .                 | 0.24-0.49                                                      | 0.24-0.50 |
|                               | Significance of difference .. | Not significant ( $t=1.52$ )                                   |           |

It can be seen that the differences are in the direction to be expected from Goldstein's theory, as schizophrenics are more "rigid". The difference only reaches significance when the test is given with a one minute time limit per card, and then the difference is not large. It is worth noting that a similar difference would tend to occur if schizophrenics have a higher proportion of incorrect answers (due to "over-inclusion") than neurotics, as the probability would then be that one of their two answers for any card would be "wrong" and thus not counted.

#### SUMMARY AND CONCLUSIONS OF EXPERIMENTS ON "CONCRETENESS"

Of the five measures of "concreteness" examined, only one differentiated the groups significantly. This was the concreteness rating based on the Goldstein Scheerer Object Sorting test. This test probably provides more scope than the others for unusual responses due to "over-inclusive" thinking, some of which are scored "concrete" if Goldstein's criteria are used. Evidence will be presented that schizophrenics do tend to produce some unusual responses on tests of this sort.

"Rigidity" has been identified with "concreteness" by Goldstein and Scheerer, but significant differences on a rigidity score only occurred when a time limit was imposed. It has been pointed out that "over-inclusive" thinking could have produced this difference equally well.

The results are at least consistent with theory that schizophrenics are not "concrete", but that they can produce "concrete" responses on some tests, if some unusual methods of dealing with the material are classified as "concrete". Since the theory of "over-inclusion" accounts for the production of unusual responses of all sorts, it is believed to offer a more useful explanation of the performance of schizophrenics on sorting tests.

#### INVESTIGATION OF "OVER-INCLUSION"

##### (a) *Results Using the Benjamin Proverbs Test*

If the concepts formed by schizophrenics are abnormally broad, it is possible that to them, a single proverb means more than it does to normal people. Thus the concept it illustrates will be more difficult to define. Several predictions can thus be made. First, before they start to answer, they will need a longer time to prepare what they are going to say. They should thus have an

increased "reaction time", if this is defined as the time elapsing between the presentation of the proverb by the examiner, and the first word spoken by the subject in answering. Second, their explanation should itself require longer to give, since it should be more complicated (more difficult), require more thought, and involve the use of more words.

The results with respect to the two time measures, are presented in Table XI.

TABLE XI  
*Time Scores (in Seconds) for the Benjamin Proverbs*

|                                    |                               |    |    |    | Schizophrenics                                              | Neurotics |
|------------------------------------|-------------------------------|----|----|----|-------------------------------------------------------------|-----------|
| "Reaction Time"                    | Mean .. .. .                  | .. | .. | .. | 26.73                                                       | 10.93     |
|                                    | Standard deviation ..         | .. | .. | .. | 19.40                                                       | 6.50      |
|                                    | Range .. .. .                 | .. | .. | .. | 5-86                                                        | 4-26      |
|                                    | Significance of difference .. | .. | .. | .. | Significant at 1 per cent. level (2 tail test) ( $t=2.90$ ) |           |
| Total time required to give answer | Mean .. .. .                  | .. | .. | .. | 68.73                                                       | 38.29     |
|                                    | Standard deviation ..         | .. | .. | .. | 28.60                                                       | 14.13     |
|                                    | Range .. .. .                 | .. | .. | .. | 33-121                                                      | 22-55     |
|                                    | Significance of difference .. | .. | .. | .. | Significant at 1 per cent. level (2 tail test) ( $t=3.60$ ) |           |

Both these time measures differentiate at a high level of significance. Six of the 18 schizophrenics obtain reaction time scores in excess of 26 seconds, and are thus completely outside the neurotic range. Ten of the 18 schizophrenics require more than 55 seconds to give their answer, once started, and are completely outside the neurotic range. These differences are unlikely to be the result of any general intellectual slowness, since none of the other speed scores differentiated so well.

The average number of words used in answering each proverb, is given in Table XII.

TABLE XII  
*Average Number of Words Used in Answering Benjamin's Proverbs*

|                               |    |    |    |    | Schizophrenics               | Neurotics |
|-------------------------------|----|----|----|----|------------------------------|-----------|
| Mean .. .. .                  | .. | .. | .. | .. | 20.93                        | 18.07     |
| Standard deviation ..         | .. | .. | .. | .. | 7.30                         | 7.56      |
| Range .. .. .                 | .. | .. | .. | .. | 12-36                        | 13-42     |
| Significance of difference .. | .. | .. | .. | .. | Not significant ( $t=1.04$ ) |           |

This difference, while in the expected direction, is not significant. It is possible that these estimates were not very reliably ascertained. It is extremely difficult, when copying down patients' answers, to avoid paraphrasing them and condensing them. This tends to occur more with people who speak at length, than those who answer briefly. It is possible that, had the answers been recorded on a tape recorder and scored later, both groups would have been found to use more words, and the differences might have been larger.

#### (b) *Results Using the Goldstein-Scheerer Object Sorting Test*

During the first stage of the administration of this test (the "Handing Over" experiment), the subjects are asked to select one of the objects on the table. The subjects are then asked to hand over to the examiner all the objects which might be grouped together with this object. As each is handed over, it is



placed out of sight by the examiner. This experiment thus requires the subject to build up a concept around the initial object. If schizophrenics tend to form over-inclusive concepts, they should select significantly more objects as belonging together during this part of the experiment.

Although Goldstein and Scheerer allow the subjects to select their own objects as starting points in this stage of the experiment, it was thought desirable to standardize this aspect of the test. In the present experiment, the "handing over" procedure was performed four times. On the first trial, the subject was allowed to select his own object. For the remaining three trials the examiner selected the object which was to be the "point of departure". The objects were always the red plate, the box of matches and the bicycle bell in that order. (Note that all subjects were given the "male" set of objects described in the manual, regardless of sex.) The over-inclusion score used was merely the average number of objects grouped together with the four objects used as "points of departure".

The results are given in Table XIII.

| TABLE XIII                                                                             |         |                                                                    |  |           |
|----------------------------------------------------------------------------------------|---------|--------------------------------------------------------------------|--|-----------|
| <i>Average Number of Objects Grouped together during the "Handing Over" Experiment</i> |         |                                                                    |  |           |
|                                                                                        |         | Schizophrenics                                                     |  | Neurotics |
| Mean                                                                                   | .. .. . | 11.33                                                              |  | 5.86      |
| Standard deviation                                                                     | .. .. . | 8.44                                                               |  | 1.66      |
| Range                                                                                  | .. .. . | 5-32                                                               |  | 4-11      |
| Significance of difference                                                             | .. .. . | Significant beyond 2 per cent. level (2 tail test)<br>( $t=2.46$ ) |  |           |

The results are in the predicted direction, and attain an acceptable level of statistical significance.

(c) *Results Using an "Object Classification Test"*

This test was originally designed to provide an easier and more objective method of measuring "concreteness" in sorting behaviour, as defined by Goldstein. The aim was to incorporate all the features of the three Goldstein-Scheerer sorting tests in one test.

The test consists of 12 small objects: four triangles, four squares and four circles. The objects vary in weight, thickness, size, material, and the hue and brightness of the colours which they are painted. There are intended to be ten different ways of grouping the objects, as follows: (1) By shape (3 groups—square, circle and triangle). (2) By size (2 groups. Some are large and some small). (3) By thickness (2 groups—half the objects are twice as thick as the others). (4) By surface area (6 groups—those of the same shape and surface size have an identical surface area). (5) Presence or absence of curved edges or corners (2 groups). (6) By weight (at least 3 groups. This sorting must be independent of density). (7) By material (3 groups—some are metal, some wood, and some a light plastic). (8) By colour (8 groups—those of precisely the same colour are grouped together). (9) By hue (four groups—some are red, some blue, some green and some yellow). (10) By saturation of colour (2 groups—some colours are highly saturated and "bright" looking, some are unsaturated and "dull" looking).

The instructions used with the test were very simple, and were as follows: "Do you see these objects on the table? I want you to sort them out into groups. Put them in some sort of order. Put those together which you think belong

together." (When S has performed one of the 10 sortings say:) "Good—Why did you do it that way?" (If the subject's explanation is correct, proceed with the test. Note that the explanation need not be completely "abstract" in Goldstein's sense, just sufficiently clear to be sure the subject has really perceived that particular sorting method. If the subject cannot explain his grouping, or if he cannot group at all, the examiner demonstrates the "shape" sorting, but does not subsequently credit it. Otherwise the initial sorting is credited. The final instructions are as follows): "Now there are other ways of sorting this material. I want you to sort the objects in as many other simple ways as you can. Arrange the objects into groups as you have just done, so that there is a single simple reason for each grouping. Each time you sort them, I want you to tell me why you have sorted them in that way." (No further instructions are given at all, but each explanation is recorded. There is no time limit. The first time the subject spontaneously says he can do no more, encourage him to continue. End the test when he gives up a second time.)

In an earlier study in which this test was used with 100 normal subjects (64) it was found that normal people are able to perceive all ten methods of sorting (although no subject saw all ten), but very seldom produce any other methods of sorting the material.

If it is true that schizophrenics are not "concrete", but are "over-inclusive", a number of predictions can be made concerning their sorting behaviour on this test. Since schizophrenics will perceive more aspects of the material as being relevant to the task than will normal people, they will be able to elaborate many more methods of sorting. These extra methods of sorting would not be considered by normal people, because they ignore the aspects of the material on which they are based (e.g. the shadows cast by the objects on the table, slight scratches on the objects, personal associations to the objects, and so on). In other words, schizophrenics have more data to work with. They should therefore take longer to do the test, because they think of more solutions. They should not distinguish between "normal" and "unusual" solutions, and should therefore produce both types of sorting in a random order. If there were no time limit to the test, there should be no reason why they should not produce as many "abstract" or "normal" methods of sorting as normal people do, although these would be interspersed among the other solutions. In practice, of course, all the subjects will tend to give up the test after working on it for a period of time, so that it would not be surprising to discover that, while schizophrenics produced many more solutions, they nevertheless produced slightly fewer "abstract" or "unusual" solutions than normal people before they gave up.

The scoring system used was simple. A "correct" response (an "A" response) was merely defined as one of the ten groupings intended in the construction of the test. Any other method of sorting (including a repetition of a previously given "A" response) was scored "Non-A".

The results obtained are given in Table XIV.

The results are as predicted. The schizophrenics obtain significantly fewer "A" scores, presumably because they "give up" the test before they have exhausted all the possibilities it has for them. On the other hand, the schizophrenics obtain significantly more "Non-A" or "unusual" sortings. Indeed 9 out of the 18 schizophrenics produced more than 8 "Non-A" sortings, the highest score for a neurotic subject.

The schizophrenics produced an average of 11.66 different methods of sorting (taking all kinds into account), while the neurotics only produced an

TABLE XIV  
*Results Using the Object Classification Test*

|                                  |                                      | Schizophrenics                                                       | Neurotics |
|----------------------------------|--------------------------------------|----------------------------------------------------------------------|-----------|
| Number of<br>"A"<br>sortings     | Mean . . . . .                       | 2.13                                                                 | 4.86      |
|                                  | Standard deviation . . . . .         | 1.77                                                                 | 1.23      |
|                                  | Range . . . . .                      | 0-6                                                                  | 3-7       |
|                                  | Significance of difference . . . . . | Significant beyond 0.1 per cent.<br>level (2 tail test) ( $t=4.78$ ) |           |
| Number of<br>"non-A"<br>sortings | Mean . . . . .                       | 9.53                                                                 | 2.21      |
|                                  | Standard deviation . . . . .         | 3.68                                                                 | 2.01      |
|                                  | Range . . . . .                      | 3-17                                                                 | 0-8       |
|                                  | Significance of difference . . . . . | Significant beyond 0.1 per cent.<br>level (2 tail test) ( $t=6.58$ ) |           |

average of 7.07 different methods of sorting. These data appear to support the theory of "over-inclusion". They certainly provide no evidence that schizophrenics are "rigid" or unable to generalize.

(d) *Results Using Epstein's Test for Over-inclusive Concept Formation*

This test was developed by Seymour Epstein (24) as a direct measure of "over-inclusion" in concept formation as defined by Cameron. The test consists of a list of 50 words printed on two pages. Following each stimulus word, there are 6 response words (including the word "none"). The subject is merely asked to underline all those response words which are an essential part of the concept denoted by the stimulus word. Epstein predicted from Cameron's theory that schizophrenics would underline more response words than normals, as their concepts would be more over-inclusive. This was, in fact, the case in his initial study.

Two scores were used in the present study. The "over-inclusion" score is based on those words which tended not to be underlined by normal people in Epstein's study. It was scored according to Epstein's own procedure so as to make the present results comparable with his.

The test also includes neologisms. Five of the 50 stimulus words are neologisms, as are 5 of the response words. A "neologism" score was calculated which was merely the total number of words (other than the word "none") underlined in response to a neologism, plus the number of neologisms underlined as responses.

It was also predicted, that, as the task would be more complicated for the schizophrenics by virtue of their more extensive and presumably more complex concepts, that they should take longer to do the test. The results obtained are given in Table XV.

The results are all highly significant, and in accordance with the predictions. It is interesting that the "over-inclusion" score appears to differentiate much better in the present study than it did in Epstein's original study. Epstein found normals to have a mean over-inclusion score of 12.49, while schizophrenics he found to have a mean of 20.92, significantly higher. The schizophrenics in the present study have a mean score over twice this size, while the neurotics score only slightly in excess of Epstein's normal group.

The "neologism" score was not used by Epstein. The significant difference on this score suggests that the over-inclusive concepts formed by schizo-



TABLE XV  
*Scores Obtained from the Epstein Test of "Over-inclusion"*

|                                                       |                            | Schizophrenics                                                     | Neurotics |
|-------------------------------------------------------|----------------------------|--------------------------------------------------------------------|-----------|
| Over-inclusion<br>score                               | Mean .. .. .               | 56.93                                                              | 16.64     |
|                                                       | Standard deviation ..      | 51.21                                                              | 16.90     |
|                                                       | Range .. .. .              | 3-157                                                              | 1-47      |
|                                                       | Significance of difference | Significant beyond 1 per cent.<br>level (2 tail test) ( $t=2.80$ ) |           |
| Neologism<br>score                                    | Mean .. .. .               | 6.00                                                               | 1.87      |
|                                                       | Standard deviation ..      | 5.05                                                               | 1.75      |
|                                                       | Range .. .. .              | 0-17                                                               | 0-5       |
|                                                       | Significance of difference | Significant beyond 1 per cent.<br>level (2 tail test) ( $t=2.97$ ) |           |
| No. of seconds<br>required to<br>complete the<br>test | Mean .. .. .               | 1161.07                                                            | 761.92    |
|                                                       | Standard deviation ..      | 415.12                                                             | 209.96    |
|                                                       | Range .. .. .              | 632-1,930                                                          | 484-1,105 |
|                                                       | Significance of difference | Significant beyond 1 per cent.<br>level (2 tail test) ( $t=3.01$ ) |           |

phrenics can incorporate words which are meaningless, but which have features in common with everyday words.

As expected, schizophrenics are significantly slower at doing the test. Again this difference cannot be explained in terms of their general intellectual slowness, since other speed scores produced very small differences.

#### (c) *Results Using the Leiter-Partington Pathways*

It was hypothesized that "over-inclusion" is due to an abnormally flat "stimulus generalization gradient" in schizophrenics. This would make discrimination learning more difficult for schizophrenics. "Set" of the "Einstellung" type can be regarded as nothing more than a special case of discrimination learning. For example, in the typical "Einstellung" rigidity test (e.g. Luchins "water jar" test (57)), in the course of a series of problems, a specific type of complicated solution is consistently "reinforced", simpler methods not being found to work. Later, when this "set" has been learned (discrimination learning) it is found that even when a simpler type of solution is possible, normal people continue to use the complex method due to their "set". If the theory is true, schizophrenic patients should *not* readily be able to learn a "set" of this type. Indeed they should not be susceptible to "Einstellung" rigidity. This lack of "set" should be an advantage in some types of tasks, and a disadvantage in others. It has already been demonstrated that schizophrenics can think of more solutions to a sorting test. In this sense they are less "rigid" and more "creative". The purpose of the present experiment was to demonstrate how this lack of "rigidity" or "set" can also be a disadvantage.

In the Leiter-Partington Pathways Test (55), the subject is presented with a series of circles randomly drawn on a piece of paper, and randomly numbered from 1 to 10. Without giving verbal instructions, the examiner with his pencil connects the circles in numerical order. The subject is then motioned (without verbal instructions) to do the same, on an identical sheet of paper. If he succeeds (as nearly all subjects do), he is motioned to do the same with a second sheet of paper (the test proper) containing many more numbered circles in a different arrangement. The authors of the test found that normal people almost never make errors on this test, and indeed they use it as an error free speed test. In

the second part of the test, the material and procedure are identical, excepting that the circles have to be connected in the order 1, A, 2, B, etc.—numbers and letters alternating.

The success of this test with normal people almost certainly depends upon the fact that when they perceive numbers being connected in order (or numbers and letters being connected), they immediately assume that the essence of the test is to connect the circles in numerical (or numerical-alphabetical) order. Presumably this strong “numerical set” has been built up through past experience. They ignore the spatial juxtaposition of the circles on the paper, and the direction of the movements the examiner makes, as they believe those to be irrelevant. However, if schizophrenics do not adopt such a normal “set”, they might well perceive these other aspects of the examiner’s performance, and elaborate some much more complex hypothesis about what the examiner is doing, involving all these aspects. However when they are given the proper test sheet, it includes many more items, and the spatial juxtaposition of the circles is now quite different. Any complex hypothesis involving both numerical arrangement *and* spatial arrangement would no longer work, since these aspects would now be in conflict. Indeed anything more elaborate than a simple numerical sequence would not be correct. It was predicted, that, if schizophrenics do form over-elaborate hypotheses for these reasons, when they tried to apply them to the test proper, they would find it very difficult. Furthermore, the conflicts produced by an elaborate hypothesis which no longer fits would lead to errors. It was thus predicted that the schizophrenics would be significantly slower, and make significantly more errors than the neurotics.

The results obtained are presented in Table XVI.

TABLE XVI  
*Results from the Leiter-Partington Pathways Test*

|                                                         |                            | Schizophrenics                                                 | Neurotics |
|---------------------------------------------------------|----------------------------|----------------------------------------------------------------|-----------|
| Errors made on<br>Pathway 1<br>(numbers<br>only)        | Mean .. .. .               | 0                                                              | 0         |
|                                                         | Standard deviation ..      | 0                                                              | 0         |
|                                                         | Range .. .. .              | 0-0                                                            | 0-0       |
|                                                         | Significance of difference | Not significant ( $t=0$ )                                      |           |
| Time in<br>seconds for<br>Pathway 1                     | Mean .. .. .               | 75.20                                                          | 69.29     |
|                                                         | Standard deviation ..      | 29.64                                                          | 30.86     |
|                                                         | Range .. .. .              | 50-172                                                         | 34-140    |
|                                                         | Significance of difference | Not significant ( $t=0.53$ )                                   |           |
| Errors made on<br>Pathway 2<br>(letters and<br>numbers) | Mean .. .. .               | 7.00                                                           | 1.86      |
|                                                         | Standard deviation ..      | 9.75                                                           | 3.76      |
|                                                         | Range .. .. .              | 0-25                                                           | 0-13      |
|                                                         | Significance of difference | Significant at 5 per cent. level<br>(1 tail test) ( $t=1.90$ ) |           |
| Time in<br>seconds for<br>Pathway 2                     | Mean .. .. .               | 123.15                                                         | 97.00     |
|                                                         | Standard deviation ..      | 62.16                                                          | 45.34     |
|                                                         | Range .. .. .              | 69-248                                                         | 51-197    |
|                                                         | Significance of difference | Not significant ( $t=1.24$ )                                   |           |

It is clear that pathway 1 did not differentiate the groups either with respect to error or time taken. This is possibly because the tests are too simple. None of the subjects made any errors at all. The time score on pathway 2 produced differences in the predicted direction, but not significant. However,

the errors on the second pathway differentiated as predicted, although only at the 5 per cent. level (1 tail test) of significance.

#### SUMMARY AND CONCLUSIONS OF EXPERIMENTS ON "OVER-INCLUSION"

For the most part, the groups were very significantly different on the measures of over-inclusion, as predicted. Of the 13 scores examined, 7 differentiated at well beyond the 1 per cent. level, while only 4 scores produced statistically insignificant differences. All the differences were in the expected direction. Individual "over-inclusion" scores differentiate the groups much better than any tests previously discussed. The results are therefore regarded as supporting the theory advanced.

#### SOME POSSIBLE CONSEQUENCES OF "OVER-INCLUSIVE" THINKING

Of all the standard cognitive tests, it was thought that the "Picture Arrangement" type of test would be most likely to be influenced by "over-inclusive" thought disorder. This test requires the subject first to perform "inductive" reasoning, and formulate some story which could account for all the pictures, before arranging them in their proper order. It was thought likely that "over-inclusive" subjects would make up over-elaborate and rather unusual stories, and thus obtain poor scores.

The test given was the Wechsler Picture Arrangement sub-test (75), and the score used was the "weighted sub-test" score. The results are given in Table XVII.

TABLE XVII

*Wechsler Picture Arrangement Scores for the Two Groups*

|                            | Schizophrenics               | Neurotics |
|----------------------------|------------------------------|-----------|
| Mean                       | 9.20                         | 10.30     |
| Standard deviation         | 2.86                         | 3.45      |
| Range                      | 5-14                         | 6-17      |
| Significance of difference | Not significant ( $t=0.93$ ) |           |

Although the results are in the expected direction, they are not statistically significant.

Rodnick and Shakow (69) have reported that schizophrenic patients are both slower and more variable in a reaction time experiment. They have explained this finding by postulating that schizophrenics are defective in maintaining a "set". This would be consistent with the theory elaborated in the present paper. Presumably schizophrenics are unable to "filter" out irrelevant incoming stimuli, and become distracted by these, making a simple reaction time task into a discrimination reaction time situation. It was proposed to investigate this theory in the present study, and an experiment designed to decrease the amount of hypothesized distraction in a normal reaction time experiment, was performed. Unfortunately any results were nullified by the initial finding. In the present group, in a simple visual reaction time experiment with no warning stimulus, the schizophrenics were slightly faster, and less variable than were the neurotics. The results are given in Table XVIII. The reaction time (expressed in tenths of a second) is the average of 10 trials, following a warm-up period of 5 trials. The variability measure used is the standard deviation of these 10 trials for each individual.



TABLE XVIII  
*Reaction Time and Variability Measures for the Two Groups*

|                              |                              | Schizophrenics                                                 | Neurotics |
|------------------------------|------------------------------|----------------------------------------------------------------|-----------|
| Reaction Time                | Mean . . . . .               | 2.46                                                           | 2.953     |
|                              | Standard deviation . . . . . | 0.39                                                           | 0.77      |
|                              | Range . . . . .              | 1.77-3.20                                                      | 1.67-4.21 |
|                              | Significance of difference   | Significant at 5 per cent. level<br>(2 tail test) ( $t=2.19$ ) |           |
| Variability of Reaction Time | Mean . . . . .               | 0.463                                                          | 0.795     |
|                              | Standard deviation . . . . . | 0.200                                                          | 0.450     |
|                              | Range . . . . .              | 0.15-0.90                                                      | 0.23-1.72 |
|                              | Significance of difference   | Significant at 2 per cent. level<br>(2 tail test) ( $t=2.58$ ) |           |

These findings are not consistent with Rodnick and Shakow's (69) findings that schizophrenics tend to be slower and more variable in reaction time. The fact that the present group contains no chronic cases could account for this discrepancy. However, it has been demonstrated on a number of tests that the schizophrenics in this study are "over-inclusive". The fact that they are faster than neurotics in their reaction time suggests that there may be no relationship between slowness in reaction time, and over-inclusive thinking. In other words, slowness in reaction time may have nothing to do with the inability to develop a "set".

#### AN INVESTIGATION OF ONE POSSIBLE EXPLANATION OF "OVER-INCLUSION"

It was postulated that "over-inclusive thinking" is due to a defect in some central "filter" which is responsible for screening out stimuli, both internal and external, which are irrelevant to the task in hand. This "filter" presumably operates by "inhibiting" these irrelevant stimuli possibly by some process similar to that described by Pavlov (63), and usually referred to as "negative induction". It is conceivable that schizophrenics are abnormal in that they do not readily develop any type of cortical inhibition. If this were the case, they should also develop "reactive inhibition" more slowly than normal people.

Eysenck (25) regards "satiation" as a special case of reactive inhibition; and has used a test devised by Klein and Krech (53) as a measure of it. This test has been described in detail elsewhere (25, 53). Briefly, it consists of a long wooden board, wide at one end and narrow at the other, which is marked off in units representing its width at that point. The subject is blindfolded and given a small block of wood to feel. His task is to estimate its width, by feeling it with his left hand, and then moving his right hand up (or down) the large board until he reaches that point at which he judges the board to be the same width as the test object. A series of 4 judgments is made initially, the score being the average. The subject is then presented with a block of wood similar to the test object, but wider. He is required to place his left hand over it, and rub it up and down for 15 seconds. This is thought to produce a "satiation" effect, so that when the subject now judges the width of the narrow test object, "displacement" will have occurred, and it will seem even narrower. If "satiation" and "reactive inhibition" are the same process, the greater the displacement effect, the more "reactive inhibition" can be assumed to have been generated. Thus the subject is asked to assess the width of the test object four times following the 15 seconds of satiation, the score being the average judgment.

The subject is then required to "sate" himself for a further 30 second period, and four more judgments are made of the width of the test object. Again more displacement should occur. Finally the subject is given a ten-minute rest, during which the "inhibition" should have dissipated. Four final judgments are taken, and the measurement of subjective width should now return to its original level.

This test was given to the two groups, and the results are presented in Table XIX.

TABLE XIX  
*Results from the Klein and Krech Figural After-Effect Test*

|                                                  |                            | Schizophrenics                                              | Neurotics  |
|--------------------------------------------------|----------------------------|-------------------------------------------------------------|------------|
| Initial judgment of width                        | Mean .. ..                 | 10.65                                                       | 10.73      |
|                                                  | Standard deviation ..      | 2.08                                                        | 2.07       |
|                                                  | Range .. ..                | 6.50-14.00                                                  | 7.75-15.00 |
|                                                  | Significance of difference | Not significant ( $t=0.11$ )                                |            |
| Judgment after 15 seconds of satiation           | Mean .. ..                 | 9.52                                                        | 8.41       |
|                                                  | Standard deviation ..      | 1.78                                                        | 1.54       |
|                                                  | Range .. ..                | 6.75-13.25                                                  | 6.25-11.00 |
|                                                  | Significance of difference | Significant at 5 per cent. level (1 tail test) ( $t=1.78$ ) |            |
| Judgment after a further 30 seconds of satiation | Mean .. ..                 | 8.15                                                        | 7.84       |
|                                                  | Standard deviation ..      | 1.66                                                        | 1.52       |
|                                                  | Range .. ..                | 5.75-10.50                                                  | 5.25-10.00 |
|                                                  | Significance of difference | Not significant ( $t=0.52$ )                                |            |
| Judgment after a 10-minute rest period           | Mean .. ..                 | 10.76                                                       | 10.66      |
|                                                  | Standard deviation ..      | 1.98                                                        | 1.29       |
|                                                  | Range .. ..                | 8.50-14.25                                                  | 8.25-13.00 |
|                                                  | Significance of difference | Not significant ( $t=0.17$ )                                |            |

The results are consistent with the theory of figural after-effects, in that, following the two satiation periods, the estimated size goes down in each group, presumably due to "displacement" effects. Following a ten-minute rest, the judgments return exactly to their pre-satiation level.

As expected, the schizophrenics consistently show smaller satiation effect than the neurotics, suggesting that they develop less inhibition. However, this difference only reaches significance after the first satiation period, and then only at the 5 per cent. level by a "one tail" test of significance.

These results are not regarded as providing unambiguous support for the theory, in that the measure of "inhibition" used makes several assumptions which may not be valid. Even if it were a valid measure of "reactive inhibition", there is no guarantee that "reactive inhibition" is related to the type of "inhibition" which the theory postulates that schizophrenics lack. Nevertheless they suggest that this aspect of the theory might profitably be investigated further.

#### SUMMARY

1. A review of the literature suggests that there is no conclusive evidence in support of the theory that schizophrenics are abnormally "concrete". On the other hand, a number of studies have clearly supported Cameron's theory that schizophrenics are "over-inclusive". No study appears to have been carried out to determine what the result would be if measures of "concreteness" and "over-inclusion" were given to the same schizophrenic group. The present study investigated this.

2. The theory of "over-inclusion" was reformulated, and a number of predictions were made from it.

3. A large battery of tests was given to 16 neurotics and 18 schizophrenics matched for age, educational attainment, Mill Hill Vocabulary Score, Progressive Matrices score and Nufferno "Level" score. The group contained no chronic schizophrenic patients.

4. Three Nufferno intellectual speed tests (A1, A2, and B1) were given under various conditions. Measures of "speed-level" discrepancy, "stress gain" and "persistence" were also obtained. Only two measures differentiated the groups significantly at the 5 per cent. level, and it was concluded that intellectual slowness is not an important aspect of schizophrenic thought disorder. It was hypothesized that intellectual slowness is a by-product of "over-inclusive" thinking in schizophrenics.

5. Four of the Babcock psychomotor speed tests failed to differentiate the groups significantly. It was concluded that motor retardation is not an important characteristic of the present schizophrenic group.

6. The following measures of "concreteness" were given: the Goldstein Scheerer Colour-Form test, the Goldstein Scheerer Object sorting test, Benjamin's proverbs test, and a test of concept formation modified from Feldman and Drasgow's test. Of five measures of "concreteness" used, only one (based on the Object Sorting test) differentiated the groups significantly. It was concluded that this result was due to the heterogeneous nature of the material, which favoured the production of unusual, "over-inclusive" responses, some of which are labelled "concrete" when Goldstein's criteria are applied.

7. "Over-inclusion" measures were obtained from the following tests: the Benjamin Proverbs, the Goldstein Scheerer Object Sorting Test, a specially designed "Object Classification Test", the Epstein test for "over-inclusion", and the Leiter-Parting pathways test. Of 13 different "over-inclusion" scores used, 7 differentiated at well beyond the 1 per cent. level of significance. Only 4 scores failed to achieve significance, but these produced differences in the predicted direction. It was concluded that these results support the theory that "over-inclusion" is a fundamental aspect of schizophrenic thought disorder.

8. There was no evidence that "over-inclusive" thinking significantly affects performance on the Wechsler picture-arrangement subtest, although this had been thought likely.

9. There was no evidence that "over-inclusion", which could produce a defect in "set", can account for slowness of simple reaction time in schizophrenia. Indeed the present group of schizophrenics surprisingly were significantly faster and less variable than the neurotics in reaction time.

10. An experiment with the Klein and Krech "figural after-effect" test produced slight evidence (significant at the 5 per cent. level) that schizophrenics show less "satiation" effect. This was related to the theory of "over-inclusion" although the results were not thought to be unambiguous.

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# SCHIZOPHRENIA: A NEW APPROACH (CONTINUED)\*

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## THE FIRST SEVEN YEARS

### *Introduction*

IN the April, 1952 issue of this journal, Osmond and Smythies (47) suggested that schizophrenia might be caused by a defect in adrenaline metabolism. They called this hypothetical adrenaline derivative "M-substance" because they endowed it with mescaline-like psychotomimetic qualities but with an effective potency nearer that of adrenaline or even the hugely powerful LSD-25. They showed that mescaline and adrenaline were sufficiently alike chemically for such an intermediate to be at least imaginable. In addition, they emphasized that the mescaline experience and the more acute and dramatic forms of schizophrenia have many similarities. They hoped that researchers would hunt diligently for our M-substance.

A second paper by Hoffer, Osmond and Smythies (33) of January, 1954 reported that adrenochrome, an immediate derivative of adrenaline, might be a suitable candidate for M-substance. This paper presents further work with adrenochrome and its close relative, adrenolutin, Lund (1949), for consideration and scrutiny. We believe that our hypothesis can now be examined and tested by anyone wishing to do so. In 1954, though we did not know it then, this was hardly possible. In the last four years many of the difficulties which existed have been or are being resolved.

1953

In June, 1953, when we (with Smythies) completed our second paper, our task appeared to be straightforward. We planned to explore the adrenochrome model psychosis, to develop an assay for adrenochrome, and to measure it in schizophrenic, other mentally ill and normal people. If we found significant differences we intended, should it be necessary, to isolate the adrenochrome in schizophrenic people and try to fulfil Koch's postulates. We hoped to examine the great illness with our new tools and use our increased knowledge to develop a rational treatment and discover ways of preventing it. Because of our inexperience, our lack of resources and suitable equipment, the generally prevailing ignorance of the catechol indoles with which we were working (for less was

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known then than we realized) and to some extent sheer bad luck, this has taken longer than we hoped. However, we have had our share of very good luck and must not sulk if the cards have sometimes been against us.

Although our main interest in recent years has been the catechol indoles in our first paper (1952), Harley-Mason made the suggestion that the primary fault in at least some schizophrenic illnesses might be due to an excessive methylation of the phenolic groups of adrenaline to produce close analogues of mescaline. Recently, Armstrong and McMillan (1957) have identified homovanillic acid and 3-methoxy-4-hydroxy mandelic acid, both derivatives of noradrenaline and adrenaline containing methoxy groups on the phenolic hydroxyl. Axelrod (1957), Resnick *et al.* (1958) have shown that this occurs in normal subjects and schizophrenics. Schizophrenics excrete about one-third of injected methyl labelled adrenaline in the urine. After marsilid about two-thirds is excreted. This inhibition of monoamine oxidase increases the excretion of adrenaline. In schizophrenics, about 60 per cent. of the injected adrenaline is not accounted for. It has not yet been shown that these compounds play any particular role either in psychoses or anxiety.

#### THE SYNTHESIS OF ADRENOCROME

We lost our source of adrenochrome early in 1953. At first we thought this merely a temporary setback because we had many kind offers to supply us with it. We soon discovered that the generosity of our benefactors was not matched by an ability to make catechol indoles. Batch after batch of adrenochrome either started to deteriorate while in transit or arrived as a mess of sticky, black amorphous melanin compounds which were too insoluble to be tested for psychotomimetic properties. The deteriorating samples could be used a few times but were unsuitable for a series of cases. We longed for the brilliant red adrenochrome which Hutcheon, Lowenthal and Eade (1956) had so skilfully made for us. For while we had no way of telling for certain, then, whether it, a by-product, derivative, or even a contaminant, was the active substance, at least we knew what we were starting with. It was suggested that a "stabilized" adrenochrome would serve our purpose, Rinkel, Hyde and Solomon (1954). This proved to be the semicarbazone which is a wholly different compound whose chemical and physiological properties do not closely resemble those of adrenochrome.

In the intervening years, we have learned something about catechol indoles and we know that they are notorious among chemists for their fugitive nature. But at that time, we were less knowledgeable and our ignorance had disturbing results. We had reports from people who had used adrenochrome unsuccessfully. We gradually realized that apart from the many other variables, neither we nor they could be certain that they were in fact using adrenochrome, or that our previous positive results came from this or some derivative of it. Recently, we have had information about other closely related compounds which seem to be quite inert. Kluver (1957) has told us of similar experiences with porphyrins. We did not know about these matters four years ago and were puzzled and discouraged. How could other people be confident that we had ever had adrenochrome, especially when we could seldom produce any? Able men have declared that it probably does not exist except perhaps transiently and that it cannot be made in pure form, while others maintained that even if it could be synthesized as a stable product the presence of ascorbic acid and other reducing substances would quickly lead to its destruction in the body. Our

unsuccessful attempts to get adrenochrome have been a source of embarrassment to us.

### THE TOXICITY OF SCHIZOPHRENIC BODY FLUIDS

While we tried to get a supply of adrenochrome with which to develop an assay method, we sought other ways of showing that a substance of this sort was present in the body. Remembering the fine work of the Machts (1956) with the shoot of the germinated lupin, we tried such varied agents as germinating wheat and oats, tomato seedlings, tadpoles, yeast and even wool. Some of these showed promise but none seemed to be worth developing. However, Fedoroff (1956) working with Professor Altschul, has perfected a cell culture test which shows a high degree of differential toxicity in schizophrenic serum, using the L-cell mouse fibroblast. This test, although too refined and difficult for routine diagnostic work, has, we think, a place in research. A number of these biological tests have been produced elsewhere during the last few years. Rieder (1957), followed by Burcell (1958), uses web-spinning spiders, Heath, Martens, Leach, Cohen and Angel (1957) and McGeer *et al.* (1957) respectively use extracts of schizophrenic serum and urine in monkeys, Winter (1957) uses injections of serum in trained white rats; Schwarzenbach (1957) has a very elegant method in which he measures changes in the germination of certain selected fungus spores. These spores respond to LSD-25, mescaline and adrenochrome in a specific manner at very low concentration. Streifler (1957) found that rat retinal tissues responded differently to schizophrenic and normal serum. However, the latest findings by Fedoroff and Hoffer (1956) that surgical patients also have toxic sera, complicates the picture, though it seems that the toxins are different in each condition. Any of these tests standing alone, as the Machts' did for so long, might be discounted by the sceptical or ignorant, but their concerted effect is to make a toxic substance seem much more probable.

### DIFFERENCES BETWEEN SCHIZOPHRENICS AND OTHERS

It follows from our hypothesis that there should be other differences between schizophrenics and those who do not have this illness. One would expect these to be associated with adrenaline metabolism and one would also expect that there would be perceptual anomalies. Hoffer (1954) has shown that 80 per cent. of schizophrenics respond differently to injections of atropine. This is of theoretical interest and compares favourably with many other diagnostic tests. It is, however, only a stopgap. Working on similar lines, Lucy (1954) showed that schizophrenics had an extraordinary tolerance for histamine and that this tolerance becomes progressively larger the longer the illness continues. Two of our patients have been able to take 75 milligrams of histamine base in one hour with little more than some discomfort. From Lucy's work, Weckowicz and Hall (1957) have developed a skin test using the speed at which a weal develops as an index of sensitivity. This clearly differentiates schizophrenics from normals and other psychiatric patients and can be done blind. He has also shown that schizophrenics are not generally unreactive as has been sometimes suggested. They respond to intradermal morphine, for instance, just as other people do. Furthermore, when nicotinic acid is given to acute schizophrenic patients for a period of two weeks, it raises the BMR more than in normal controls given the same amount, Hoffer and Callbeck (1957). These explorations suggest that both acute and chronic schizophrenics

are a continuum and that long-stay patients are still pharmacologically active and not "burnt out" as has sometimes been thought. Adrenochrome itself is an antihistamine, Hutcheon *et al.* (1956). Lea (1955), following Lucy's work, gave a very elegant demonstration that allergies are far less frequent in schizophrenic soldiers than in a comparable group suffering from head injuries and suggested that a raised level of blood adrenochrome was responsible. Ehrenthel (1957) reports the same findings and gives a long list of other such reports.

Weckowicz (1957) and Crookes (1957) have shown that chronic schizophrenic patients have marked disturbance in the constancy of their visual perception which is in keeping with their time perception as shown by Lhamon and Goldstone (1956). It is curious that even now we know very little about the world in which schizophrenic persons live. There has been much talk about sensitive and empathic insights, etc., but very little maintained and co-ordinated effort to measure the perceptual difficulties of schizophrenic people. Yet one would suppose that such disabilities could have marked effect on their behaviour.

#### ADRENOLUTIN

In their initial work, Eade (1954) with Hutcheon drew our attention to 3,5,6-trihydroxy-N-methyl indole which has been called adrenolutin. In 1954, while visiting J. Harley-Mason in Cambridge, one of us (A.H.) was again reminded of its existence. Harley-Mason gave us a small bottle containing about 200 milligrams of it which he had had on his shelves for nearly two years. This was all that he had at that time. The adrenolutin consisted of smooth running, shining golden crystals which had a greenish sheen when looked at askew. They dissolved easily in water and were very stable in solution. Indeed this could be boiled without decomposing. We felt this would be much easier to work with than fugitive adrenochrome.

Accordingly, as we reported elsewhere, Hoffer (1957), we started to work with adrenolutin, using it orally on human volunteers because at that time we had no experimental animals available. The new compound seemed to be a powerful psychotomimetic and had the unexpected ability to spread its effect over several days, lasting sometimes a week or more. At first, we thought this was improbable but after it was repeated several times we had to reconsider our views. Our small store of adrenolutin soon ran out but since we knew that Harley-Mason was ready to make us more when we needed it, we did not preserve our original supply. Indeed as soon as we asked for a new lot, he was as good as his word and sent it. For the next two and a half years we saw no adrenolutin resembling that 200 milligrams. The second sample was an amorphous, khaki coloured powder and more than two years was spent in a series of frustrating and usually futile attempts to get either pure adrenolutin or adrenochrome. At times we almost began to wonder whether these substances were hallucinations rather than hallucinogens. The experts were polite but on the whole, sceptical. Yet we knew that we had seen them and experienced their effects but it was not easy to convince other people who had not had our experiences.

In 1955 and 1956, we did a series of double-blind experiments using the best samples of adrenolutin then available to us. There seemed no doubt that susceptible people gave a characteristic response. But our sample was not active enough to affect every subject. Yet we were loath to increase the dose



because some subjects had prolonged responses lasting a week or more. Consequently, many of our findings, although interesting and highly suggestive, were not really suitable for statistical evaluation. Meanwhile our chemist colleagues continued to struggle with the synthesis of adrenolutin which now proved to be at least as difficult as that of adrenochrome. Indeed we made large quantities of the latter substance some months before the former. It is not easy to convey our disappointment during these hard months when we had tantalizing glimpses of a promised land. We were lucky that work by others, less direct than our own but no less valuable, gave us encouragement, and our therapeutic trial with niacin heartened us a little.

#### NIACIN TREATMENT IN SCHIZOPHRENIA

We had always hoped that our new approach would help in developing a rational treatment for schizophrenia. In 1952, following observations on some preliminary cases, we started then as we have reported elsewhere, Hoffer, Osmond, Callbeck and Kahan (1957), a sustained trial of our new treatment. This consisted of massive doses of niacin or its amide ranging from 3 to 25 grams daily. We will not discuss this work in detail here. Table I from our recent paper outlines our results. These are that while niacin seems beneficial in early schizophrenia and apparently reduces the rate of relapse (one out of thirty-seven, viz. six out of thirty-six) when medication is continued, it is usually ineffective in long-continuing illnesses. An exciting and unexpected by-product of this nicotinic acid work has been the discovery, Altschul, Hoffer and Stephen (1955), now confirmed by Parsons and others (1956) at the Mayo Clinic, that nicotinic acid in large doses reduces the level of cholesterol in the blood. Further it will, as Altschul (1955) has shown, protect rabbits against artificially induced arteriosclerosis. Niacinamide, which is equally effective in schizophrenia, does not do this.

TABLE I  
*Effect of Nicotinic Acid on Treatment of Acute Schizophrenia*

| Treatment in Hospital | Follow-up Treatment | Number of Patients |    | Certified to Mental Hospital During Follow-up | Suicides |
|-----------------------|---------------------|--------------------|----|-----------------------------------------------|----------|
| Nicotinic acid        | Nicotinic acid      | ..                 | 24 | 1                                             | 0        |
| Other treatment       | Nicotinic acid      | ..                 | 13 | 0                                             | 0        |
| Nicotinic acid        | Other treatment     | ..                 | 36 | 6                                             | 0        |
| Other treatment       | Other treatment     | ..                 | 98 | 47                                            | 4        |

#### THE METABOLISM OF MESCALINE

Smythies, while holding a Nuffield Fellowship at Cambridge, collaborated with Harley-Mason and Laird (1957) on the problem of the mode of action of mescaline. The large effective dose of this compound, the slow mode of onset of its effects and the fact that it is quickly fixed to liver protein and during the phase of psychosis (or equivalent period in mice) little is to be found in the brain suggests that the active agent is either some metabolite of mescaline or a toxic bodily metabolite with whose detoxication mescaline interferes. Their findings were that 35 per cent. of the mescaline is excreted unchanged in the urine within 24 hours, only a trace in the second 24 hours and none after that. A specific metabolite, 3-methoxy 4,5-dihydroxyphenylacetic acid was also

isolated in small amounts in a conjugated form. The rest of the mescaline was unaccounted for. Thus the problem of the cause of the "mescaline" psychosis remains unsolved.

#### WORK IN OTHER CENTRES BEARING ON OUR HYPOTHESIS

The rise of tranquilizers, many of which have been developed from antihistamines or from *Rauwolfia* derivatives, was interesting to us, more so because recently it has been suggested that their main effect is on adrenaline metabolism. Their mode of action is still obscure and they have thrown very little light on the aetiology of schizophrenia. From our viewpoint the work of Heath and Leach has shown the greatest boldness and imagination. Its details are still disputed, but only the most bigoted or pedestrian could fail to recognize that the extraction from the blood of schizophrenic patients of a protein fraction which itself acts as a psychotomimetic is a notable happening. That these findings should have been greeted with a combination of open ill will, irritation, scepticism and intolerance, reflects the muddled state of many psychiatrists. This response was due in part to an inability by some workers to reproduce these results. This must have been due to technical failures as confirmation has now been reported by the KABI group in Sweden (1957). It seems that there may be in schizophrenic blood at least one aberrant protein fraction, which is closely related to ceruloplasmin and has been called taraxein by Heath and Leach. This substance seems to play a part in the metabolism of amines and increases the excretion of indoles in urine, Heath *et al.* (1958). We do not yet know exactly what takes place and more recent work indicates that the suggestion that only ceruloplasmin is responsible for the conversion of adrenaline to adrenochrome is not correct, Payza and Hoffer (1958). However, differences in detail and the fact that it has not always been easy to separate taraxein does not reduce the importance of this work. Heath's and Leach's emphasis on the enzymic mechanisms complements our interest in the substrates and products with which they are concerned.

In 1954, a major objection to our hypothesis was that the body did not seem to produce enough adrenaline to form the quantities of adrenochrome, adrenolutin or derivatives required to produce model psychoses in our experiments. While there are other factors which we have discussed elsewhere, Hoffer and Osmond (1955), and will touch on later in this paper, Elmadjian and Hope (1957) and Gaddum, Krivoy and Laverty (1958) have shown that more adrenaline is made in the body than was previously supposed. Furthermore, local production of adrenaline analogues near neurones and the rate of turnover of adrenaline may be important factors independent of the blood level.

Since 1954, in addition to "adrenochrome" and "adrenolutin", other indolic or potentially indolic substances have been found to be psychotomimetic. Harmine, Pennes and Hoch (1957), and ibogaine, Schneider and Sigg (1957) have had these properties reaffirmed. TMA, Peretz, Smythies and Gibson (1955), has been added by one of us. Bufotenin, Fabing *et al.* (1956), has received some attention, while Sherwood's (1957) BGE and Szara's (1957) two compounds, dimethyl and diethyl tryptamine, give continuing support to our suggestion that of the known psychotomimetics most are indolic or potentially indolic substances. Table II shows those known in 1954 and those now known.

Although the psychological activity of adrenochrome and adrenolutin

## TABLE II

*Psychotomimetic Substances*

|               |                                           |
|---------------|-------------------------------------------|
| A. 1954:      | Mescaline                                 |
|               | Lysergic acid diethylamide                |
|               | Harmine                                   |
|               | Ibogaine                                  |
|               | Hashish                                   |
|               | Adrenochrome                              |
| B. 1958:      | Adrenolutin                               |
|               | Dimethyl tryptamine                       |
|               | Diethyl tryptamine                        |
|               | T.M.A.                                    |
|               | Bufotenine                                |
|               | Lysergic acid monoethylamide              |
|               | Lysergic acid morpholide                  |
|               | The German's green compound               |
|               | B.G.E.                                    |
|               | 3, 4 methylene hydroxy phenisopropylamine |
|               | Methyl tryptamine                         |
|               | Psilocybin                                |
| C. Delerients | Acetyl lysergic acid                      |
|               | Methyl lysergic acid                      |
|               | WIN 2299                                  |
|               | Aboud's compounds                         |
|               | Nalline                                   |

in humans is not readily recognized by those who have had little experience with a variety of psychotomimetics, their effect on animals is easily demonstrable. Adrenochrome placed in the cerebral ventricles of cats in dosages of  $\frac{1}{2}$  to 2 mg. produces marked catatonic and trance-like states, Schwarz *et al.* (1956), Rice and McColl (1957). It is interesting that in all these experiments adrenochrome synthesized by C. Pfizer and Company or in Saskatchewan was used. Adrenochrome markedly inhibits the performance of trained climbing rats, Winter (1957), distorts the web pattern of the garden spider, Witt (1954) and produces clear catatonia in pigeons, Wojcicki and Hoffer (1957), and monkeys, Melander (1957). It does not, however, seem to be effective in mice, Smythies (1958). Such interspecies differences, however, are not in the least uncommon.

It is sometimes forgotten, especially by those mainly engaged in working with animals, that the great majority of people with schizophrenia do not suffer from catatonia. Most of our patients, particularly in the early stages of their illness, are noteworthy for the fleeting nature of their symptoms. Indeed, so difficult has it been to characterize exactly the early psychological changes of this illness that psychologists still disagree about the value of psychological tests in diagnosis, in spite of a vast literature which bears witness to the great efforts that are being made to find suitable ones. So those aspects of our work with adrenochrome and adrenolutin which seem least satisfactory to researchers keen for an imposing array of statistically significant tests are the ones which give particular plausibility to the possible role of psychotomimetic agents in schizophrenia. In well run hospitals florid symptoms have always been far rarer than in badly run ones, and when they occur they are often transient.

## FURTHER WORK IN SASKATCHEWAN

Curiously, some authors who could not have read our papers carefully have foisted on us the notion that all indoles are psychotomimetic or con-



versely, that we consider only indoles or potential indoles can be psychotomimetic. Having ascribed to us a viewpoint we do not support, they have then demolished this with irrelevancies. What we have done is to present evidence that most of the proven psychotomimetics whose active principles are known have, so far, been indoles or potential indoles, with the exception of the still disputed active principles of hashish and Abood's new atropine analogues, WIN 2299 and nalline.\* Furthermore, we have, of course, never maintained that adrenochrome, adrenolutin or such other active derivatives as may be found, were the sole cause of schizophrenia. We have recognized at least two main groups of factors (1) those leading to increases in parasympathetic function and increased acetylcholine levels, and (2) those leading to increased quantities of adrenaline indoles or similar indoles. These are minimum conditions. One set of factors alone will undoubtedly yield some mental disorder but both are required for a clear demonstration. So far with the exception of hashish about which we do not have the necessary data, WIN 2299 and nalline, the psychotomimetic substances listed in Table II resemble either adrenaline or adrenochrome in structure. Abood's (1958) atropine-like compounds and atropine itself increases the production of adrenaline as do the acetylcholine esterase inhibitors.

To reproduce an acute severe schizophrenic psychosis (omitting for the moment the extremely important matter of social setting), both aspects of the model are required. This might be done by injecting large quantities of acetylcholine, which is difficult, or by inhibiting the choline esterase, which is simple. A combination of choline esterase inhibitor with adrenochrome and/or adrenolutin should accomplish this. Melander (1957) using this type of potentiation experiment, found that cats which did not respond clearly to 100 micrograms of LSD-25 alone, or to 5-10 mg. adrenolutin alone (100 mg. of adrenolutin will induce catatonia) became catatonic when given a small quantity of adrenolutin ninety minutes after 100 gamma of LSD-25 (5 to 10 mg. per cat).

Melander's contribution provides us with a method of inducing psychotic-like experiences of short duration, which has not always been possible. We have repeated Melander's work with cats, in humans using LSD-25 as the sensitizing agent and adrenochrome or adrenolutin as the psychotomimetic agent. Our normal subjects (more than twelve) showed little response to 35 micrograms of LSD-25 by mouth. After one and a half hours they were given 10 milligrams of adrenochrome by vein. Adrenochrome levels are assayed before LSD-25, before the adrenochrome, thirty and sixty minutes after adrenochrome has been given.

The clinical response after the 35 gamma of LSD-25 was slight and consisted mainly of an increase in tension. There was no alteration in adrenochrome levels. While the adrenochrome was being injected, a remarkable feeling of muscular weakness set in, there was some constriction of the chest and a need for deep breathing. This continued for some minutes. A few minutes later, a typical adrenochrome or adrenolutin experience begins. But this is sometimes as intense as that seen with 100-200 micrograms of LSD-25 and continues from five to nine hours. The experience is not an intensification of the usual LSD-25 experience but is an intensification of the adrenochrome

\* The published accounts of WIN 2299, Nalline and Abood's atropine derivatives suggest that their effects are not wholly similar to mescaline, LSD-25, adrenochrome, etc. Clouding, confusion and some drowsiness occurred. However, testing procedures for some psychotomimetics in humans are hardly refined enough for one to be dogmatic.

experience. With normals and alcoholics, we have found (1) changes in perception which include visual disturbances such as slight movement of objects, distortions, colour changes, difficulties in judging the distance and size of objects, changes in the perceived body and changes in time perception; (2) changes in thought with blocking, concreteness, paranoid thinking, feelings of passivity, social disinhibition; (3) fluctuations in emotions ranging from severe depression with suicidal ideas to transient euphoria; (4) inappropriate activities; and (5) catatonic features such as gross muscular weakness, shuffling gait, motor inco-ordination and negativism.

After the injection of adrenochrome, blood levels are elevated three- or four-fold but return to normal within two hours although the experience continued.

LSD-25 in psychotomimetic doses increases adrenochrome levels up to four-fold within two to four hours of administration, Hoffer (1958). It also blocks acetylcholine esterase, especially pseudocholine esterase. Thus LSD-25 on its own produces both conditions. At present, pseudocholine esterase is generally supposed to play only a small part in the transmission of nerve impulses. The finding that LSD-25 blocks pseudocholine esterase, Thompson *et al.* (1955), more effectively than choline esterase suggests that this should be reconsidered. Pseudocholine esterase may have an important role in normal brain function.

2-Bromo LSD which does not produce an LSD psychotomimetic experience also blocks pseudocholine esterase and thus reproduces the first set of conditions. However, it does not elevate adrenochrome levels and the second set of conditions is not fulfilled. We have pre-treated two subjects with  $\frac{1}{2}$  mg. BOL followed one and a half hours later by 10 mg. of adrenochrome. When the adrenochrome is injected the immediate reaction is similar to subjects pre-treated with LSD-25 but instead of the experience increasing in intensity, it decreases and within the hour there was no residual change. Adrenochrome levels were normal half an hour and one hour after injection. When BOL is given alone, the level of adrenochrome does not rise as it does after LSD-25.

We have found that LSD-25 stabilizes adrenochrome in blood *in vitro* and also increases the conversion of adrenochrome into adrenolutin, Hoffer (1958). Apparently the pathway leading to leuko-adrenochrome is blocked. In plasma, the conversion of adrenochrome to leuko-adrenochrome is probably enzymatic and is accelerated by adding ascorbic acid *in vitro*. LSD-25 may specifically inhibit this enzyme. The adrenochrome levels remain high for 48 hours after LSD-25 has been given. If ascorbic acid is given during the experience the adrenochrome levels stay within the normal range but there are marked fluctuations with some rebound in 24 hours. These two observations strongly suggest that LSD-25 also blocks conversion of adrenochrome into leuko-adrenochrome *in vivo*. It seems likely that the high adrenochrome levels are produced by this inhibition of adrenochrome destruction rather than by an increased secretion of adrenaline.

Taraxein also potentiates adrenolutin, Heath (1958), and may do so by stabilizing adrenochrome.

Hoff (1957) reports that serum from 500 ml. of blood taken from a normal subject one and a half hours after receiving 100 mg. of LSD-25 produced an LSD-experience when injected into another normal person. This serum could only contain much less than 10  $\mu$ g. LSD-25, but there would be larger quantities of adrenochrome, adrenolutin and other substances.

## THE ROUTE OF ADMISSION OF PSYCHOTOMIMETICS

There are many clues which emphasize not only the importance of the route but the manner of giving psychotomimetics—it is odd that this has had so little attention in recent years. The special preparations for smoking hashish or opium, the elaborate arrangements for snuffing cohoba, the complicated method of chewing the betel nut, even the careful steeping of tea or coffee, all emphasize the importance of proper preparation. While in the Kava-Kava ceremony we have evidence of an animal enzyme, ptyalin, being used to liberate an active principle. This is even clearer in the unusual methods of the Chuckchees in Siberia in preparing *Amanita muscaria*. It is doubtful whether many of us would relish the honour of drinking great draughts of our host's urine, however stimulating the results might be.

In our first experiments with "adrenochrome" we used subcutaneous injections\* because we thought it would disintegrate in the stomach and we were not sure enough of its effects to use the intravenous route. When we later used "adrenochrome" intravenously for the first time, our subject, Mr. Charles Jillings, experienced great pain along the course of the brachial vein which seemed to be of an anginal type. He bore this courageously and was not nearly as distressed as his colleagues. We later found that if "adrenochrome" solution was mixed with blood before injection this did not happen. We started using "adrenolutin" orally because our first sample had not been tested on animals. Later we used "adrenolutin" by mouth and by vein. We have also tried it as a snuff by nasal inhalation without effect.

In mid-1956 (as we have reported in this journal) Osmond and Hoffer (1958), we learned that oral inhalation might be more effective than by other routes. Since then, we have experimented with impure "adrenolutin", mixed adrenaline derivatives and pure adrenochrome solution, using a simple de Vilbiss No. 33 hand sprayer. These experiments have been suggestive. We have also used a Riker Medihaler (supplied by the courtesy of the Riker Corporation, Los Angeles), an ingenious device which delivers a measured quantity of aerosol adrenochrome suspended in Freon gas. Preliminary results suggest that adrenochrome by this route is many times more powerful than when given by vein. It is not easy to see why adrenochrome injected into the ante-cubital vein about 18 inches away from the lungs should be so much less effective than when squirted into them directly. It would appear that adrenochrome must be destroyed or bound by the venous blood in some way. It seems likely that a few dozen gamma at the most reach the brain direct from the lungs and they have a very disorganizing effect. The importance of this becomes clear when one realizes that in acute schizophrenia and LSD model psychoses the level of free adrenochrome in the blood seems to be of the same order that might occur in these inhalation experiments. These must clearly be repeated and greatly expanded, for they have unusual possibilities. It almost looks as if adrenochrome, when given this way, is as powerful as when instilled into the ventricles. Yet this is simpler, safer and involves no surgery. Recently Taubmann and Jantz (1957) have shown that adrenochrome by the sublingual route given in doses from 3–6 mg. produces a marked response. We have, ourselves, confirmed this now in five cases. This work is extremely important and interesting

\* These quotation marks indicate that the substances we used at that time did not have the high chemical purity that is now possible but were a red mixture of adrenaline oxidation products certainly containing large quantities of adrenochrome; while adrenolutin was a yellow-green mixture often very high in adrenolutin, sometimes not high at all.



and emphasizes once more the need for much greater attention to the route of administration.

### PURE ADRENOCROME AND ITS CONSEQUENCES

It now seems that until early 1957 neither we nor anyone else could be sure that they had ever possessed pure adrenochrome. Indeed, some have openly and repeatedly averred that it does not and cannot exist. We did not possess such omniscience, but we have been very uneasy from time to time. A chance meeting which one of us (A.H.) had with Dr. Atcheson in Vancouver resulted in our being given a valuable clue. It is well known among indole chemists that indoles are very sensitive to even small quantities of metallic ion. Less than one part in a thousand may act as a catalyst so that the whole compound becomes unstable. Dr. Atcheson suggested that they might play a part in this instability. This has proved to be so and, working in our laboratory, Payza has already made micro quantities of pure crystalline adrenolutin. Shortly after this, he and Heacock (1958) succeeded in making much larger quantities of pure stable adrenochrome. This has brilliant dark red, lanceolate crystals which remain stable in air indefinitely and whose solution in distilled water is also very stable. About the same time, Abood (1957) discovered an enzymic way of making pure adrenochrome. Our information was passed on to Melander of the KABI group in Sweden and they are now making adrenochrome and adrenolutin in quantity. Adrenolutin purified of all adrenochrome and metallic ions appears once again as golden yellow stable crystals, like those originally synthesized by Harley-Mason.

Once we had obtained a pure supply of adrenochrome further advances became possible. Payza and Hoffer (1958) have already shown that it is synthesized in the body from adrenaline by an enzyme called adrenaline oxidase which they readily distinguished from ceruloplasmin. Adrenochrome is unstable in serum and turns either to leuko-adrenochrome Hoffer (1957), in the presence of ascorbic acid, or adrenolutin in the presence of ions of heavy metal. Adrenolutin does not combine with ascorbic acid but Melander (1957) has shown that it very readily combines with ceruloplasmin. Perhaps this combination of ceruloplasmin and adrenolutin can be disrupted by Heath's taraxein leaving adrenolutin free. Ostfeld, Abood and Marcus (1958) have shown that only analogues of his new hallucinogen that raises the blood level of ceruloplasmin are hallucinogens. Furthermore, subjects who fail to react to this new hallucinogen with hallucinations do not show this rise in blood ceruloplasmin. Payza and Mahon\* (1958) have only recently perfected a method of measuring adrenochrome levels in blood and are currently attempting to do the same for adrenolutin and leuko-adrenochrome. This is in itself of great interest, but what is even more important is we may reasonably expect to discover new ways of measuring the by-products of adrenaline metabolism. Tests of pure adrenochrome and adrenolutin will help to show whether these are psychotomimetic substances in themselves or whether our previous results and the psychotomimetic effects of pink adrenaline were due to breakdown products of these substances. We do not yet know, however, how complicated these metabolic patterns may prove to be.

### ADRENOCROME METABOLISM

A survey of adrenochrome plasma levels in all psychiatric patients shows there is no significant difference between them. However, schizophrenic patients

\* Method available on request.

have more adrenochrome in their cerebrospinal fluid than do other patients. Patients who are anxious and tense have lower than normal levels. The ratio of adrenochrome in cerebrospinal fluid to plasma, both drawn simultaneously, is 1.9 for schizophrenics (N=15), 0.9 for people with depression and anxiety (N=7) and about 1.1 for medical and surgical patients.

Adrenochrome is more stable in cerebrospinal fluid *in vitro* than it is in plasma. It is therefore not surprising that the levels are higher in schizophrenic cerebrospinal fluid and not in plasma.

Adrenochrome may be destroyed less rapidly in schizophrenics and form larger quantities of adrenolutin. To test this possibility an adrenochrome tolerance test was developed. This is similar in principle to the intravenous glucose tolerance test. This test has been given to schizophrenic patients, subjects not schizophrenic and normal volunteers after they were given LSD-25. These results are shown in Table III.

TABLE III  
*Tolerance for Ten Milligrams Intravenous Adrenochrome*

| Group                    | N | Initial<br>Level<br>μg./litre | Per cent. Change at |               |               |
|--------------------------|---|-------------------------------|---------------------|---------------|---------------|
|                          |   |                               | 15<br>(mins.)       | 30<br>(mins.) | 60<br>(mins.) |
| Schizophrenic .. ..      | 6 | 43                            | +280                | +75           | +107          |
| Not schizophrenic .. ..  | 9 | 51                            | +170                | -45           | -23           |
| Normal 35 μg./LSD-25* .. | 6 | 48                            | +260                | +100          | +67           |
| Normal 100 μg./LSD-25 .. | 2 | 46                            | —                   | —             | +170          |

\* 2 hours before adrenochrome test.

The schizophrenic patients destroyed adrenochrome more slowly than other subjects and in this way resembled subjects pre-treated with LSD-25.

LSD-25 given to subjects causes an increase in adrenochrome levels, Hoffer (1958). When the adrenochrome levels are markedly elevated the experience is strongly visual with little tension. When there is little increase in adrenochrome the experience is characterized by extreme tension and anxiety with minimal visual changes. BOL-148, a substance that does not elevate adrenochrome, does not produce any unusual experience.

TABLE IV  
*Effect of LSD-25 and BOL-148 on Adrenochrome Levels in Plasma With and Without Ascorbic Acid Treatment*

| Group                | N | Treatment                                                           | Adrenochrome μg./litre |     |     |     |     |    |
|----------------------|---|---------------------------------------------------------------------|------------------------|-----|-----|-----|-----|----|
|                      |   |                                                                     | 0                      | 2   | 4   | 6   | 24  | 48 |
| Normal and alcoholic | 7 | LSD-25 100-300 μg. ..                                               | 66                     | 227 | 216 | 139 | 117 | 74 |
| Normal               | 2 | LSD-25 100 μg. 5 grams ascorbic acid before LSD                     | 84                     | 170 | 115 | —   | 84  | —  |
| Normal               | 3 | LSD-25 100 μg. ascorbic acid before and during LSD experience .. .. | 68                     | 74  | 59  | —   | 82  | 54 |
| Normal               | 4 | BOL-148 500 micrograms ..                                           | 82                     | 59  | —   | —   | —   | —  |

The evidence provides strong support to our contention that adrenochrome metabolism is disturbed in schizophrenia.

## DISCUSSION

1. *A New Approach and Research Method*

More money is now available for research in psychiatry and scientists such as biochemists, organic chemists, pharmacologists, neurophysiologists, etc., are being drawn in. Much of this new work is aimed at the biological aspects of schizophrenia in the hope of relating specific biological disturbances to special psychological abnormalities. We must, if we are to use the scientific method, construct an hypothesis and test it vigorously by trying to refute it. When planning research of this sort there is a hierarchy of hypotheses which must be borne in mind.

One hypothesis is that schizophrenia derives from a specific biological fault of either metabolism or cybernetic function of the nervous system. A counter hypothesis to this is that of at least some psychoanalysts who hold that the disturbing factors are primarily psychological and that anyone subject to a particular spectrum of conditions in early childhood will develop this illness. The biological hypothesis suggests a specific genetic fault. As we have observed, an advantage of our hypothesis is that we can include psychological stress factors in the biological aetiology, since if the metabolic fault is in the biochemical mechanism subserving the organism's response to environmental stress, if this mechanism is overloaded, breakdown must result.

A research programme based on psychoanalytic procedures can hardly avoid being less efficient than one based on biological investigations for several reasons.

1. After nearly sixty years, there is little evidence of a scientific sort deriving from experimental and statistical procedures that the psychoanalytic hypotheses are true. There is even less that they are of use in the understanding and treatment of schizophrenia. Indeed, there is some doubt among psychoanalysts themselves as to how far their theories apply to the illness.

2. The theoretical structure of psychoanalysis as a science is primitive. It describes a series of "entities"—"Ego", "Super-ego", "Id", etc., which are supposed to have certain properties and inter-relations. There are, of course, no such entities, and the whole system is a convenient way of describing behaviour, dreams, fantasies, etc., and their inter-relations by means of metaphor disguised as analogy and passed off as fact. This is not uncommon in the early stages of any science and may be found in 18th century chemistry when it was bedevilled by the phlogiston theory, or in general medicine in the days of Brown, Broussais and Stahl.

3. Even if we admit that psychoanalysis has some scientific status, this must still be judged primitive for two further reasons. First, it lies at a lower level in the positivistic hierarchy than biochemistry, its rival from our point of view. For psychological explanations are to be reduced, by the laws of the hierarchy to which psychoanalysis, claiming to be a science, must subscribe, to more fundamental physiological and chemical explanations and not vice versa. Amongst other things "more fundamental" implies in medicine "more useful in devising new treatments" for it is in treatment that medical theories are tested. Secondly, as Popper (1958) points out, the theories of psychoanalysis can be plausibly applied to all human behaviour. They are susceptible to all manner of "confirmation". But because they are really descriptions masquerading as explanations and because of their generality and their many escape clauses, such as reaction formation, they cannot be refuted. So far, they have been of low predictive value, but even if this were not so it is by their



irrefutability that they cease to be scientific theories, for every scientific theory can, in principle, be refuted.

However, while one may favour a biological approach, the question is which one and at what level? There are two main hypotheses to choose from, the cybernetic and the pharmaco-biochemical. The former implies that schizophrenia is due to a failure in the brain mechanism brought about by inherent faults in design. One can imagine that so complex a mechanism could have its own mode of breakdown like those found in computers, due to the failure in cybernetic organization rather than metabolism. This fascinating hypothesis is not yet testable because we are still so very ignorant about the cybernetic function of the brain. We do not know yet how the millions of neurones co-operate in their computing and classificatory functions. The micro-electrode only tells us about a few neurones, while the EEG gives us the summated activity of several millions. Smythies (1958) has recently suggested a new way of tackling this problem. But even so, apart from crude methods like E.C.T. and lobotomy, no therapeutic intervention in the cortical circuits is yet possible. So this approach, although of great theoretical interest, seems difficult and unlikely to lead to therapeutic advances. We come then to the hypothesis that the disease may be due to an error in chemical metabolism. Such an error could result in faulty electrical behaviour and cybernetic function of the brain, leading in turn to psychological and social disturbances.

A chemical hypothesis can be subdivided into three main possibilities.

(a) The excessive or *de novo* production of a toxic metabolite causing illness by the disruption of intermediary metabolism (cf. phenylketonuria).

(b) The relative or complete absence of a necessary metabolite (cf. diabetes).

(c) The lack of balance between a pair of complementary systems.

These three possibilities must be subdivided into conditions in which a fault occurs in the brain and is limited to it and those in which the whole body is involved. These faults could be either genetic or acquired as a result of exhaustion of the mechanisms underlying stress, and negative emotions such as guilt or feelings of inferiority, or to a combination of both.

One is faced with looking for a metabolic fault. What should one look for? Literally millions are possible, which should be investigated? There are in fact only two choices. One can be guided by a strong hypothesis (which will be specific, based on known facts, able to explain these facts and will be testable) or a weak hypothesis which will not be able to explain known facts, hard to test; in short a shot in the dark.

The history of science indicates that one should only resort to a weak hypothesis in desperation when no strong one is available. Indeed, the only function of a weak hypothesis is to gather facts for developing a strong hypothesis. For instance, an example of this procedure would be to measure all manner of physiological variables in schizophrenia (i.e., blood cholesterol, iron, cobalt, vital capacity, steroid hormones, etc.) in the hope of finding deviations from normal which would suggest an hypothesis. A less extreme example would be to re-examine those numerous tests said to be positive in schizophrenia and to find correlations between them. Although this might be valuable as a preliminary, it is clearly inefficient to do so while strong hypotheses exist and until they have been refuted decisively by experiment.

Our New Approach adapts Koch's postulates to a metabolic illness. We have asked the following questions:

1. "What chemicals can produce a clinical state resembling schizophrenia?" We then noted a number of substances which could do this.

2. "Which of these chemicals resemble more or less closely known human metabolites?" We then noted the relationship between mescaline and adrenaline. This led at once to an initially strong hypothesis that the metabolism of adrenaline or a relative such as serotonin is at fault in schizophrenia. The strong hypothesis must then be subjected to the usual tests to see whether it accounts for known facts and allows one to predict new ones accurately.

At the moment, only the serotonin, the adrenaline oxidation product hypotheses and the acetylcholine hypothesis can be considered strong, and they may be reducible to a common hypothesis.

Table V shows the known aberrant facts about schizophrenia in 1954 when two of these hypotheses were first made public and the facts which have since been gained; showing the predictive success of each.

TABLE V

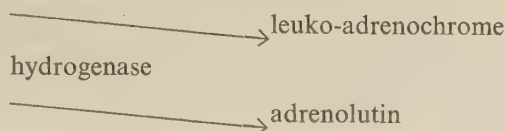
| Known Facts                                                                 | Does Model Account for this |                                                                 | How |
|-----------------------------------------------------------------------------|-----------------------------|-----------------------------------------------------------------|-----|
|                                                                             |                             |                                                                 |     |
| 1. Genetic factors                                                          | Yes                         | Abnormal enzymes (e.g. adrenochrome reductase).                 |     |
| 2. Stress factors                                                           | Yes                         | Increase in adrenaline, therefore of adrenochrome.              |     |
| 3. Stress amelioration therapeutic                                          | Yes                         | Decreased production of adrenochrome.                           |     |
| 4. Self perpetuating                                                        | Yes                         | See equations. Adrenochrome inhibits choline esterase.          |     |
| 5. Negative association allergic illness and increased resistance histamine | Yes                         | Adrenochrome antihistaminic.                                    |     |
| 6. Negative association asthma and conversion one into other                | Yes                         | Assume lack of adrenaline in asthma. Adrenochrome would be low. |     |
| 7. Negative association diabetes mellitus                                   | Yes                         | Adrenochrome strong anti-insulinase.                            |     |
| 8. Increased pigmentation                                                   | Yes                         | Adrenochrome precursor of melanin pigments.                     |     |
| 9. Response to ET, Niacin, ascorbic acid                                    | Yes                         | Decreased production and increased destruction of adrenochrome. |     |
| 10. Choline esterase inhibitors contra-indicated                            | Yes                         | See equations.                                                  |     |
| 11. Sympathomimetic amines contra-indicated                                 | Yes                         | See equations.                                                  |     |
| 12. Different indoles in urine                                              | Yes                         | See equations.                                                  |     |
| 13. Positive association growth disturbances                                | Yes                         | As above.                                                       |     |
| 14. Positive association with tuberculosis                                  | Yes                         | Adrenochrome antimitotic for fibroblasts.                       |     |
| 15. Increased resistance thyroid                                            | Yes                         | Adrenochrome is anti-thyroid.                                   |     |

We therefore urge with Bain that the resources available for the biological aspects of psychiatric research should be directed in the main to studying the metabolism, physiology, and pathogenesis of adrenaline, serotonin and of enzymes such as ceruloplasmin and adrenaline oxidase, as well as searching for new psychotomimetic agents chemically allied to known human metabolites. For there is no reason why the group of schizophrenias should not develop from sev-



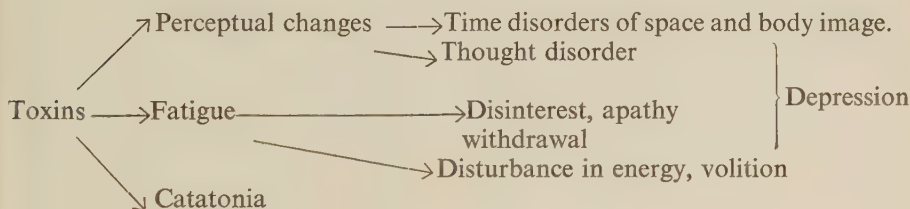


## 3. Adrenochrome reductase



There are at least two factors in our model, increased acetylcholine and increased amounts of indoles or allied catechol, quinone or methylated amines which otherwise resemble adrenaline. It is probably modified by other variables. Pseudo-choline esterase seems to play some special part in psychic activity for it is blocked preferentially by that most potent hallucinogen LSD-25. Substances which block choline esterase alone produce psychological changes only when administered in such large amounts that other changes may mask this, such as DFP, etc. With LSD-25 both conditions are met for adrenochrome levels are increased. BOL-148, which blocks choline-esterase but does not increase levels (see Table IV) is not psychotomimetic.

Third order variables result from these previous changes. It may be that some clinical and psychological changes are affected by two main sorts of disturbances, (a) Sensory—changes in perception and (b) Motor—usually marked fatigue and inertia but sometimes great energy and excitement due, of course, in each case to the toxins of the disease. This may be illustrated:



In our opinion the very disorganizing effect of changes in perception, especially those connected with changes in perception of the self and levels of reality has received far too little attention. The schizophrenic person with an impaired sense of self and reality must surely find social adjustment increasingly difficult. Once the web of mutual expectations and obligations which hold us in social contact with our fellows is disrupted, isolation results. As communication between the sick person and his group becomes more tenuous, a greater or lesser degree of alienation occurs, so that communication may never again be re-established. Alienation may lead to a solitary life outside a mental hospital or to expulsion and incarceration. The outcome depends not only on the sex, age, temperament, physique and intelligence of the sick person, but also on the customs, tolerance and sophistication of the community. Thought disorder requires much exploration—but it is not easy to imagine that “normal thinking” would persist when perception of time has been greatly changed—let alone the many other perceptual modes.

The three sets of variables inter-react. For instance, perceptual changes may make a parent look strange or hostile, which will increase stress variables aggravating in turn those of the second and third order. It is a balanced system

where alteration in one set of variables results in a shift in the whole. We believe this model accounts for schizophrenia better than other ones. To illustrate this we have listed data about schizophrenics generally agreed to by psychiatrists who consider that these patients are suffering from an illness and not simply from a faulty reaction formation.

### 3. *The Way Ahead*

Perhaps this is the place to state unequivocally that we do not claim that our hypothetical M substance is identical with either adrenochrome or adrenolutin. They are only two out of many possible immediate derivatives of compounds lying between tyrosine and leuko-adrenochrome. What we do claim is that they are the first (and indeed at present the only) candidates for M substance which can be obtained as pure stable chemicals and for which there is evidence that they are both psychotomimetic and can occur in the human body. A full study of adrenochrome and adrenolutin both in and out of the body may lead us to even more promising candidates.

Taubmann (1937), Abood (1958), Sherwood (1957) and our own observations suggest that a variety of chrome indoles and amines exist which require the most careful study. Adrenochrome and adrenolutin are the only two so far which our tests suggest are present in the body, but this does not of course mean that they are necessarily the only ones to be found. We should not dogmatize as to whether substances can or cannot exist in the body simply because we cannot make them in the test tube, for this may reflect more on our chemical ineptitude than on any inherent difficulty of synthesis *in vivo*. The last fifty years have shown repeatedly that a substance may be important even though hard to synthesize and to assay. Our evidence suggests that many so-called "inactive" substances may have to be reconsidered. One can reasonably ask, "Inactive in what context?" A very powerful pressor substance may be a very sluggish psychotomimetic and vice versa. In the present state of knowledge no derivative of adrenaline should be acquitted of activity—a verdict of not proven will encourage frequent revision of status as tests for different sorts of activity are discovered. It is misleading to judge activity only in terms of a particular quality, such as its effect on leech muscle, without a proviso that there are other sorts of activity.

To make full use of the discoveries now being made another set of prejudices, which have in recent years acquired much unwarranted respectability, must be discarded. This is the notion that the effects of mescaline, LSD-25, adrenochrome, etc. more closely resemble toxic confusional rather than schizophrenic illnesses. Attempts to differentiate between a toxic confusional (delirious) and schizophrenic condition on a clear-cut "either/or" basis suggests a greater precision than is yet possible. Pretensions of this sort, for all their superficial attraction, are unscientific. What one finds is a continuum with clouding of consciousness and confusion at one end and disturbances in thinking and mood at the other, with changes in perception sometimes present and sometimes absent. In such a continuum over-lap is likely and this is what is found.

Schizophrenia and the effects of mescaline or LSD-25 can be compared in terms of similarity or difference, depending upon the requirements of the observer. We have found that similarity has been useful, but it is surely time to jettison the misleading, meaningless, though frequently repeated statements that the effects of LSD-25, mescaline, adrenochrome, etc., are "only toxic

states". Louis Lewin (1931), the father of psychopharmacology, long ago emphasized that the mescaline experience did not resemble a delirium. Less exact observers than he, claiming an undeserved authority, have greatly added to the difficulties of those who work with these substances by confusing the issue. The work now being done makes it essential that we have a deep knowledge of these schizophrenic-like experiences. As we have noted elsewhere there is no prospect that the clinical illness, schizophrenia, will ever be reproduced experimentally, because, in our view at least, an ethical experimenter would not be able to duplicate the necessary psychosocial conditions.

While our main interest lies with this great illness whose nature we have been exploring, we are aware that the discovery of a new group of active metabolites of adrenaline may have repercussions reaching beyond schizophrenia and indeed outside psychiatry. Fascinating though these are, we shall not discuss them here.

### CONCLUSION

Only modest effort is now required to test our hypothesis. Adrenochrome can be made and measured both *in vivo* and *in vitro*. Adrenolutin can be made but cannot yet be measured accurately. The enzymes which convert adrenaline to adrenochrome are known and we know something about the way by which adrenochrome becomes adrenolutin and leuko-adrenochrome. These substances have been or are being tested by a variety of routes in both animals and humans. Radioactive techniques should help in exploring the metabolism of these adrenaline derivatives. Once we understand their metabolism better it may be possible to prevent their formation, to neutralize their effects if they are formed or to hasten their destruction in the body. In this way we may combat a great disease and extend our knowledge of body and mind. We hope that our model of schizophrenia will be used, tested and finally, when it has been replaced by a better, discarded. Like any other scientific hypothesis, it is a step cut in the melting ice of history to let us climb a little higher. It is not a niche for an idol.

### SUMMARY

The authors discuss the last five years work of the Saskatchewan group and develop their hypothesis relating adrenaline metabolites to schizophrenia. They also discuss work done in other centres. They indicate some of the difficulties encountered not only in synthesizing adrenochrome and adrenolutin but also in working experimentally with them in human subjects. The successful synthesis of pure stable adrenochrome and adrenolutin has made chemical assay possible. Using their adrenochrome assay, they have found differences between adrenochrome metabolism in normals and schizophrenics. While these require exploration the authors believe that their hypothesis is strong enough to warrant attention or to see whether others can confirm their findings. While adrenochrome and adrenolutin are at present the only metabolites of adrenaline which can be obtained as pure stable compounds and have psychotomimetic properties, there is suggestive evidence that others will be found.

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# \*INDOLURIA IN SCHIZOPHRENIA:

## I. STATISTICAL STUDY AND INVESTIGATION OF HEPATIC FUNCTION

By

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### INTRODUCTION

INVESTIGATION of the urinary excretion of indoles in psychotic illnesses has a certain historical precedent. Thus Townsend (1905) and Bruce (1906) reported excess of indican in the urine of melancholic patients. Bruce correlated this finding with the recognized tendency to constipation in depressives and treated his patients with enemata. Ross (1913) reported that schizophrenic subjects excreted an excess of indole-acetic acid in the urine. De Jong (1945) reported the experimental induction of catalepsy in cats by the intravenous administration of indolethylamine and noted in his monograph that this substance, if perfused *in vitro* through the liver, is converted to indole-acetic acid. Buscaino (1952) reported finding abnormal amounts of primary and secondary amines in the urine of schizophrenics. More recently Riegelhaupt (1956, 1958) has reported an excess of tryptophan metabolites in schizophrenic urine while McGeer and co-workers (1957) have reported a difference in the excretion of aromatic substances as between normals and schizophrenics. Though these authors do not make the point clear, yet in fact indoles come under the general heading of aromatic substances.

There are currently three main chemical concepts of schizophrenia. The first theory, that an abnormal oxidation product of adrenaline might be the endogenously produced toxic substance involved, was promulgated by Osmond and Smythies (1952). A further report (Hoffer, Osmond and Smythies, 1954) described experiments with adrenochrome. However, their results were not confirmed (Rinkel *et al.*, 1957). Further reports by Hoffer (1957a, 1957b) on the hallucinogenic effects of adrenolutine were somewhat equivocal.

The second theory, proposed by Woolley and Shaw, that schizophrenia might result from an excess or a deficiency of the neurohormone serotonin (5 hydroxy tryptamine) remains a hypothesis but has resulted in considerable research into serotonin and other tryptophan metabolites.

The third concept, that of Heath and his co-workers (1958), implicates a circulating toxic substance which they have named Taraxein. They isolated this substance from schizophrenic serum and found that they could produce schizophrenic symptoms by injecting the extract into healthy volunteers. It has been suggested that the substance may be a globulin. As yet there has been no confirmation of their findings by other workers.

This present investigation is based on somewhat different ideas. It seems to the author that a specific endogenously produced toxic factor in schizophrenia would be biologically improbable. An analogy with diabetes mellitus

\* Based on work already submitted for the Degree of M.D. at the University of St. Andrews.



might be illustrative. With the discovery of insulin the aetiology of diabetes seemed clear but in fact this has proved to be far from the case. A defect in the secretion of insulin by the Beta cells of the pancreas is certainly an important factor but only one factor in a complex system for maintaining this particular aspect of homeostasis. Similarly in schizophrenia, if we are in fact dealing with a biochemical disorder, it seems likely that the defect will be a complex one and one involving more than one anatomical system.

There are certain theoretical grounds for believing that the current interest in tryptophan and its metabolites may not be misplaced. Tryptophan has, of course, an indole nucleus and shares this feature with the majority of known hallucinogenic substances. Serotonin is synthesized in the body from ingested tryptophan and is known to have some role in brain function (Brodie *et al.*, 1955). In fact serotonin shares with noradrenaline the function of synaptic inhibition in experimental preparations, measuring impulse transmission across the transcallosal synapse in the cat (Marrazzi and Hart, 1955). These "neuro-hormones" also share another feature, that of being inactivated by the same enzyme, monoamine oxidase. It may also be relevant that reserpine, one of the most powerful neuroleptics used in the treatment of schizophrenia, appears to work through the release of serotonin from its usual "bound" form (Pletscher *et al.*, 1956).

As mentioned earlier, there are historical grounds for this re-emergent interest in tryptophan metabolites. However, the work of Bruce and Townsend was severely criticized by Easterbrook (1906) and, in fact, the theory of auto-intoxication fell into disrepute until resuscitated in sophisticated form in relation to hepatic encephalopathy (McDermott and Adams, 1954). Recent work in this field (Dawson *et al.*, 1957; Phear *et al.*, 1956) suggests that hepatic coma may be due to the absorption of toxic substances from the small intestine, the result of bacterial action on ingested protein. In the patients under discussion there is, of course, the particular factor of a portal-systemic shunt so that blood can travel straight to the cerebral circulation without passing through the liver.

A recent paper by Summerskill (1958) advocates the use of neomycin to depress the activity of the bacterial flora, plus a low protein intake and purgation. It should be made clear that constipation *per se* is irrelevant. The site of the bacterial action is the small gut where the absorption of toxic protein breakdown products also occurs. It could be objected that hepatic encephalopathy bears little clinical or symptomatic relationship to schizophrenia. This is, of course, true but the question of hepatic dysfunction in schizophrenia has in fact been the subject of extensive research. The Quick Test, in which administered benzoic acid is coupled with glycine to form hippuric acid which is then excreted in the urine, was employed by Quastel and Wales (1940). These authors found a low excretion rate in 100 per cent. of 18 catatonic patients and 15 per cent. of other schizophrenics studied. However, their findings were not confirmed (Greville, 1945). The Cephalin-Cholesterol Flocculation Test (C.C.F.T.) was found by Buscaino (1952), De Jong (1945) and Shattock (1950) to give a high proportion of positive results in schizophrenia, especially the catatonic subgroup. However, Zimmermann and co-workers (1948) and Smith (1954) reported essentially negative results. Of interest in this connection was the report by Patzig and Block (1953). These workers injected mice with mescaline labelled with  $^{14}\text{C}$  and found that the mescaline was rapidly bound to liver protein. After a time interval, which would correspond to the delay before mental changes (i.e. hallucinations) are experienced in man, they

sacrificed some of their animals and found that the brain content of mescaline was surprisingly low. They suggested that the protein-mescaline complex might be the cause of the mental symptoms or alternatively that the adsorption of mescaline on to liver protein might block sites normally available for the detoxication of endogenous toxins. It is relevant also that the first stage in the metabolism of tryptophan, namely that of ring substitution at position 5, giving 5-hydroxy tryptophan, is effected in the liver. The enzymatic processes involved have been investigated in animals (Udenfriend *et al.*, 1956).

The oxidative catabolism of tryptophan can proceed along the aromatic or the quinolic pathways. The former is initiated, again in the liver, by a labile enzyme system which is composed of tryptophan peroxidase and an oxidase which produces hydrogen peroxide as a product of its activity (Knox and Meyler, 1950). The content of the tryptophan oxidizing system present in liver is commonly low. It can be increased by feeding tryptophan (Williams and Elvehjem, 1950) and by administering adrenaline, which is believed to act via the pituitary-adrenal axis (Knox, 1951).

The author believes that the observations outlined above provide a basis for thinking that tryptophan metabolism may be implicated in the aetiology of schizophrenia or more particularly some schizophrenics. He suggests that once again a complex series of interlocking mechanisms will be involved. At the very least dietary differences, intestinal function and flora, hepatic function and probably adrenal function will be implicated and require study.

This paper describes a statistical comparison of indoluria in schizophrenics and other groups and a re-investigation of hepatic function in schizophrenia using the Cephalin-Cholesterol Flocculation Test.

## EXPERIMENTAL OBSERVATIONS

### PART 1. STATISTICAL STUDY

The object of this part of the study was to compare the amount of indole substances excreted in the urine by different "populations". While it was appreciated that there is likely to be considerable day to day variation in such excretion patterns, it was only practicable to examine one specimen from each subject. The specimen in each case was the "night urine", that is the first urine passed on waking in the morning. Initially it was planned to collect all the urine passed between 8 p.m. and 8 a.m. However, so many of the early specimens had to be discarded as being incomplete that it was decided merely to examine the first morning specimen. It should be noted that the different "populations" were not comparable as to situation, diet or fluid intake. The specific gravity was measured on the first fifty specimens and was found to range from 1012 to 1020. However, as there appeared to be no correlation between the specific gravity of the urine and the indole content, this practice was discontinued.

### *Materials*

The "normal population" consisted of 25 male and 20 female doctors and nurses. The mean age was  $32.6 \pm 9.2$  years.

The "Female schizophrenic population" consisted of 34 patients resident in the wards of the Royal Edinburgh Hospital. The mean age was  $57.2 \pm 10.5$  years.

The "Female non-schizophrenic psychotic population" consisted of 20 patients also in the hospital. The mean age was  $55.85 \pm 12.8$  years.

The diagnosis in these 54 patients was confirmed by study of the case notes and discussion with Dr. S. Gray.

The "Mental defective population" consisted of 25 female patients in Gogarburn Hospital. The mean age was  $38.7 \pm 14.5$  years. The diagnosis in each case was supplied by courtesy of Dr. R. Bailey, Physician Superintendent.

The "Male schizophrenic population" consisted of 61 patients resident in the wards of the Royal Edinburgh Hospital. The mean age of this group was  $47.4 \pm 11.6$  years.

The "Male non-schizophrenic psychotic group" consisted of 50 patients also resident in the Royal Edinburgh Hospital. The mean age of this group was  $52.8 \pm 16.5$  years. These patients were all under my care at the time of the observations and the diagnosis in each case was checked by personal observation and reference to the case notes.

The "Medical population" consisted of 25 male and 25 female patients under treatment at Bangour General Hospital. The diagnoses were supplied to me by courtesy of Dr. Wright under whose care these patients were at that time (1956). The mean age of this group was  $50.4 \pm 12.6$  years.

### *Methods*

The two-way ascending chromatographic method employed was based on that described by Jepson (1955). As a matter of convenience a smaller tank and aluminium frame were employed, made by Messrs. Shandon Ltd. This frame carried square papers (20 cm.  $\times$  20 cm.) which did not permit of a very wide separation of the "spots". The difficulty was overcome to some extent by using Whatman No. 1 paper.

The solvent used for the first run was Isopropanol-ammonia (Isopropanol 200 ml. + water 20 ml. and ammonia 10 ml.). For the second run Butanol-acetic acid was employed (n-butanol 120 ml. + water 50 ml. + glacial acetic acid 30 ml.).

The origin was marked in pencil 2 cm. from each edge in the lower right-hand corner of each paper. The patient's name and the date were recorded on the top right-hand corner and the paper was then fitted on to the frame. Filtered urine was then "spotted" on to the origin using a micrometer pipette (Messrs. Shandon's) in 5-10 microlitre portions. The spot was dried between each application using an electric hair drier. A total of 100 microlitres was applied. The frame employed carried twelve papers, the last one in each run being a "reference paper". On to this paper had been spotted 10 microlitres of a mixture containing urea, tryptamine hydrochloride, serotonin creatinine sulphate, indolyl acetic acid and tryptophan (1 mg. per ml. of each substance).

The first solvent (Isopropanol-ammonia) was then poured into the aluminium tray, the frame placed in the tray and the lid replaced. The "run" was allowed to proceed overnight (10 hours) the frame was removed and the solvent blown off using a hair drier. The tray and tank were then washed, the tray filled with butanol-acetic acid and the frame replaced but at right angles to the first position. This run was permitted to continue for 6-7 hours. This solvent was then blown off and the papers, still on the frame, were thoroughly dried.

The papers were then removed from the frame and were dipped through the Ehrlich location reagent. This was made from a 10 per cent. w/v solution of p-dimethylaminobenzaldehyde in concentrated hydrochloric acid. Just before use 10 ml. of this solution was mixed with acetone 40 ml. (this amount



lasted 4-5 papers). The reagent was poured into a polythene tray and the papers were rapidly drawn through the liquid. The papers were then dried by means of the hair drier (though latterly facilities became available in the Royal Edinburgh Hospital Pathology Laboratory, including the use of a fume cupboard) and examined flat on pieces of white paper. The "spots" were outlined in lead pencil as they appeared.

The Rf. values, as Jepson remarked in his paper, are not very constant using the technique but the relative positions of the indole substances are very constant. It was found that a large amount of urea in the urine caused a spreading "spot" which pushed indoxyl-sulphate ahead of it and thus displaced indoxyl-sulphate beyond its expected Rf. position. This point is also noted by Ivor Smith (1958). Also as a matter of economy the same solvent was used for two "runs". Such "old" solvents appeared to alter the Rf. values but the relative positions remained unchanged.

Rf. values were measured using a perspex device described by Bloch *et al.* (1958) and constructed according to their instructions by the author.

TABLE I

| Substance                     | Range of Rf. ( $\times 100$ ) |        |
|-------------------------------|-------------------------------|--------|
|                               | IPr. Am.                      | Bu. A. |
| Urea                          | 40-48                         | 45-55  |
| Tryptamine hydrochloride      | 72-80                         | 60-70  |
| Serotonin creatinine sulphate | 42-50                         | 48-57  |
| Tryptophan                    | 20-30                         | 45-55  |
| Indolyl-acetic acid           | 35-40                         | 86-92  |

The colour reactions given by the Ehrlich dip are quite characteristic and taken in conjunction with the Rf. values give a fair idea of the probable nature of the "spots" found. In addition the time of appearance was helpful. Thus urea always appeared first and its central position provided a good "marker". Next a blue-purple spot with slightly greater Rf. values than urea appeared; this quickly faded to grey (later referred to as spot QFB). Meanwhile the characteristic orange of indoxyl sulphate appeared, then the slow purple of tryptophan and indolyl-acetic acid. Tryptamine was only seen on the reference papers. It appears about the same time as indoxyl sulphate.

It should be made clear that in this part of the project no attempt was made to identify spots. It was decided somewhat arbitrarily (on the basis of Jepson's paper) that normal urine may contain urea, indoxyl sulphate and tryptophan. These "spots" bear a fairly constant relationship to each other. Any other "spots" showing a reaction in the blue-purple-red range to Ehrlich's reagent constituted the grounds for allocation to the "excess indole excretion" group. This criterion permitted the separation of all the urine examined into the two categories "normal excretion" and "excess indole excretion".

## PART 2. INVESTIGATION OF LIVER FUNCTION USING CEPHALIN-CHOLESTEROL FLOCCULATION TEST

### Material

This consisted of 29 male and 19 female schizophrenic patients resident in the wards of the Royal Edinburgh Hospital. There is considerable overlap between this group and that used for the indoluria study. The new patients used in this group were either under the immediate care of the author or of

Dr. S. Gray and the diagnosis of schizophrenia was confirmed. There were 12 catatonics, 22 hebephrenics and 14 paranoid schizophrenics in this group. The mean age was  $41.4 \pm 7.1$  years and the mean length of illness was  $15.6 \pm 11.2$  years.

### Methods

1. Five ml. of venous blood was withdrawn from the arm veins at approximately the same time each day (10–11.30 a.m.) from each patient. The blood was collected in a plain tube, allowed to clot and then centrifuged for five minutes.

2. Five ml. of anaesthetic ether was added to a bottle of cephalin-cholesterol antigen (prepared by Difco Laboratories, Detroit, Michigan). This was then kept in the refrigerator.

3. Thirty-five ml. of distilled water was brought to the boil in a 100 ml. beaker. To this was added, in parts and with stirring, 1.0 ml. of the ether-antigen mixture. The beaker was then kept on the electric hot-plate with further stirring of the mixture until the volume had been reduced to 25 ml. This constituted the "working solution".

4. To 4 ml. of 0.85 per cent. saline in a test-tube was added 0.2 ml. of patient's serum and 1 ml. of "working solution". The test-tube was inverted twice to ensure thorough mixing and was then left, uncorked, in a rack in a dark cupboard.

5. Readings were taken at 24 and 48 hours. If the emulsion remained as a homogeneous suspension the result was negative. In the case of a positive reaction the lipoid tended to flocculate and precipitate to the bottom of the tube. Complete precipitation leaving a clear supernatant fluid was classed as 4 plus. Lesser degrees were classed as 1 plus, 2 plus, 3 plus. The results were checked by consultations with Miss J. A. B. Darling, a biochemist working in the laboratory and accustomed to the details of the test.

## RESULTS

### Part 1

As explained under "Methods", night urine samples were examined from 95 schizophrenic subjects, 70 non-schizophrenic psychotic subjects, 50 "medical subjects", 25 mental defectives, and 45 "normals".

The chromatographic results were classified, according to criteria already described, into those showing Excess Indole Excretion (E.I.E.) and those not showing E.I.E. Fifteen out of the 50 "medical subjects" showed E.I.E. (30 per cent.) and 7 out of the 25 mental defectives (28 per cent.). The results for the other groups are shown in Table II.

TABLE II  
*Incidence in Different Groups of Excess Indole Excretion*

| Population                             | No. of<br>Subjects | Mean<br>Age | S.D. | No.<br>with<br>E.I.E. | Per<br>cent.<br>with<br>E.I.E. |
|----------------------------------------|--------------------|-------------|------|-----------------------|--------------------------------|
| Schizophrenic males .. ..              | 61                 | 47.4        | 11.6 | 32                    | 52.5                           |
| Non-schizophrenic psychotic males ..   | 50                 | 52.8        | 16.5 | 22                    | 44                             |
| "Normal" males .. ..                   | 25                 | 35.9        | 9.9  | 2                     | 8                              |
| Schizophrenic females .. ..            | 34                 | 57.2        | 10.5 | 12                    | 35.3                           |
| Non-schizophrenic psychotic females .. | 20                 | 55.85       | 12.8 | 4                     | 20                             |
| "Normal" females .. ..                 | 20                 | 29.2        | 9.4  | 5                     | 25                             |

Applying the  $\chi^2$  formula to the figures for the male schizophrenic and male non-schizophrenic psychotic groups (using Yates correction) gives a value of 0.4929,  $N=1$ . This is not significant at the 5 per cent. level.

On the other hand the difference between the "normal" males and the other two male groups is significant at the 5 per cent. level (Table III).

TABLE III  
*Observed Frequencies: Male Groups*

|             |    | Normal | Schizophrenic | Non-Schizophrenic Psychotic | Total |
|-------------|----|--------|---------------|-----------------------------|-------|
| With E.I.E. | .. | 2      | 32            | 22                          | 56    |
| No E.I.E.   | .. | 23     | 29            | 28                          | 80    |
| Total       | .. | 25     | 61            | 50                          | 136   |

*Expected Frequencies: Male Groups*

|             |    | Normal | Schizophrenic | Non-Schizophrenic Psychotic | Total |
|-------------|----|--------|---------------|-----------------------------|-------|
| With E.I.E. | .. | 10.3   | 25.1          | 20.6                        | 56    |
| No E.I.E.   | .. | 14.7   | 35.9          | 29.4                        | 80    |
| Total       | .. | 25     | 61            | 50                          | 136   |

$$\chi^2=8.68. \quad N=2.$$

Applying the  $\chi^2$  formula to the figures for the female schizophrenic and female non-schizophrenic psychotic group (again using Yates correction) gives a value of 0.9475,  $N=1$ . This is not significant at the 5 per cent. level. Similarly the difference between the "normal" and other two female groups is not significant at the 5 per cent. level (Table IV).

TABLE IV  
*Observed Frequencies: Female Groups*

|             |    | Normal | Schizophrenic | Non-Schizophrenic Psychotic | Total |
|-------------|----|--------|---------------|-----------------------------|-------|
| With E.I.E. | .. | 5      | 12            | 4                           | 21    |
| No E.I.E.   | .. | 15     | 22            | 16                          | 53    |
| Total       | .. | 20     | 34            | 20                          | 74    |

*Expected Frequencies: Female Groups*

|             |    | Normal | Schizophrenic | Non-Schizophrenic Psychotic | Total |
|-------------|----|--------|---------------|-----------------------------|-------|
| With E.I.E. | .. | 5.7    | 9.6           | 5.7                         | 21    |
| No E.I.E.   | .. | 14.3   | 24.4          | 14.3                        | 53    |
| Total       | .. | 20     | 34            | 20                          | 74    |

$$\chi^2=1.06. \quad N=2.$$

There is an apparent difference in incidence of E.I.E., as between the male and female populations. The difference is not significant at the 5 per cent. level (Table V).



TABLE V  
*Observed Frequencies: Male and Female Populations*

|             |    |    |    | Male | Female | Total |
|-------------|----|----|----|------|--------|-------|
| With E.I.E. | .. | .. | .. | 56   | 21     | 77    |
| No E.I.E.   | .. | .. | .. | 80   | 53     | 133   |
| Total       | .. | .. | .. | 136  | 74     | 210   |

*Expected Frequencies: Male and Female Populations*

|             |    |    |    | Male | Female | Total |
|-------------|----|----|----|------|--------|-------|
| With E.I.E. | .. | .. | .. | 49.8 | 27.2   | 77    |
| No E.I.E.   | .. | .. | .. | 86.2 | 46.8   | 133   |
| Total       | .. | .. | .. | 136  | 74     | 210   |

$$\chi^2=2.15. \quad N=1.$$

Finally the question of the relationship between age and E.I.E. has been considered (Table VI).

TABLE VI  
*Showing Per cent. Incidence of E.I.E., in 5 Year Age Groups*

| Age Groups     | No. in Age Group | No. with E.I.E. | Per cent. Incidence E.I.E. |
|----------------|------------------|-----------------|----------------------------|
| 20-24 .. .. .  | 13               | 1               | 7.7                        |
| 25-29 .. .. .  | 18               | 3               | 16.7                       |
| 30-34 .. .. .  | 15               | 6               | 40                         |
| 35-39 .. .. .  | 23               | 12              | 52.2                       |
| 40-44 .. .. .  | 22               | 9               | 40.9                       |
| 45-49 .. .. .  | 19               | 9               | 47.4                       |
| 50-54 .. .. .  | 19               | 6               | 31.6                       |
| 55-59 .. .. .  | 26               | 11              | 42.3                       |
| 60-64 .. .. .  | 18               | 6               | 33.3                       |
| 65-69 .. .. .  | 12               | 5               | 41.7                       |
| 70-74 .. .. .  | 12               | 5               | 41.7                       |
| 75-79 .. .. .  | 7                | 2               | 28.6                       |
| 80-84 .. .. .  | 4                | 2               | 50                         |
| 85-89 .. .. .  | 2                | 0               | 0                          |
| Totals .. .. . | 210              | 77              | 0                          |

It is likely that the 50 per cent. incidence of E.I.E., for the age group 80-84 is a distortion due to the few subjects (4) in the group. The two other "peaks" at 35-39 and 45-49 probably reflect the age distribution among the male schizophrenics. On the whole the table suggests that there is little correlation between age and E.I.E., in the subjects studied.

### *Part 2. Cephalin Cholesterol Flocculation Tests*

In accordance with the criteria for positive reactions, as outlined under Methods, four positive results were observed. The serum from two patients gave results rated as 2 plus and serum from a further two patients gave results rated as 1 plus. Thus the per cent. incidence of positive results in these 48 patients was 8.3 per cent. Two of the patients giving positive results were from the catatonic subgroup and two from the hebephrenic subgroup, representing a percentage incidence for the two groups of 16.7 per cent. and 9 per cent. respectively. It should be noted that when this flocculation test is used for

suspected liver disease a 1 plus result is often disregarded. If this practice were applied to the present findings the incidence over the series of 48 subjects would fall to 4.15 per cent.

#### DISCUSSION

The statistical study reported here, involving 285 subjects, confirms that more subjects excreting excess indoles were found among the schizophrenics than among the other group studied. Only in one case, however, was the difference in incidence significant at the 5 per cent. level, namely the difference between the "normal" male, male psychotic and male schizophrenic groups. Another way of interpreting the figures would be to say that whereas there are marked differences between different members of the population regarding the amount of indolic substances excreted in the urine, yet no very marked correlation appeared between excess indole excretion and age, sex or diagnostic category. This might alternatively indicate that the schizophrenic group is heterogeneous from the aetiological standpoint.

Or it might reflect defects in the experimental methods. Admittedly the psychiatric diagnoses were only checked personally in the case of the male schizophrenic and male non-schizophrenic psychotic groups. The patients in the female groups were under the immediate care of Dr. S. Gray and the diagnosis in each case was discussed by the author with Dr. Gray. The diet differed as between the psychiatric, medical "normal" and defective subjects. Many of the patients were on neuroleptic drugs. However, there is evidence that reserpine by mouth in the usual therapeutic doses has no effect on indole excretion (Forrest, 1957). Todrich and co-workers (1958) have shown a rise in the rate of excretion of 5 H.I.A.A., after I.M. reserpine (5 mg.) but this only lasted a matter of 4-8 hours. In regard to chlorpromazine the author has studied five schizophrenics before and during treatment (300 mg. per day by mouth) and found no change in the pattern of excreted indoles. This has been confirmed by Buscaino and Stefanachi (1958), and could have been predicted from the work of Brodie *et al.* (1956). These workers found that serotonin-releasing activity was limited to certain tranquillizers belonging to the Rauwolfia group.

Notwithstanding these objections the author feels that the results of this study indicate that within the group designated schizophrenic there is a subgroup excreting an excess of indole substances. These findings are in keeping with those of Riegelhaupt (1958) and McGeer and co-workers (1957). A more recent paper by Rodnight and Aves (1958) reported that the mentally ill subjects studied showed a higher total of indole spots on their urine chromatograms than did the "normal" or "medical" subjects. Whether this suggested difference in indole excretion bears any aetiological relationship to mental illness requires more elaborate evidence. As Horwitt (1956) has pointed out, many of the supposed differences between schizophrenic and non-schizophrenic subjects may be due to environmental artifacts. The investigation of hepatic function in 48 schizophrenic subjects using the Cephalin-Cholesterol Flocculation Test gave essentially negative results. Hanger (1939) who introduced this test examined 900 normal subjects and got only one positive result. The test has been extensively used in schizophrenia. De Jong (1945) reported 46.8 per cent. of positive results in catatonics and lower figures for other schizophrenics. He also reported 6.9 per cent. of positive results in his controls. Negative results were, however, reported by Zimmermann *et al.* (1948) and Smith (1954).

These differences may reflect the improved dietary and physical health of hospitalized schizophrenics over the past 15 years. This is the sort of environmental artifact to which Horwitt referred in his paper. However, Richter (1957), reviewing the work on liver dysfunction in schizophrenia, concluded that whereas there is no evidence that hepatic dysfunction is an obligatory concomitant of schizophrenia yet we are not in a position to exclude the possibility of disturbance at an enzymatic level.

#### SUMMARY

1. A chromatographic study of urine samples from 285 subjects revealed a higher incidence of subjects excreting excess indoles amongst the schizophrenics.

2. The differences in incidence were only significant at the 5 per cent. level as between the male "normals", male schizophrenics and male non-schizophrenic psychotics.

3. Cephalin-Cholesterol Flocculation Tests were performed on 48 schizophrenic subjects. Positive results were obtained in 8.3 per cent. of cases. This incidence is not considered to be significant.

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# \*INDOLURIA IN SCHIZOPHRENIA:

## II. CHROMATOGRAPHIC STUDY ON 40 SCHIZOPHRENIC AND 10 NORMAL SUBJECTS

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### INTRODUCTION

In Part I of this communication the theoretical basis for the investigation was outlined. Details of a statistical study were given and it was suggested that these confirmed a greater incidence amongst schizophrenics than normals of subjects excreting an excess of indole substances. In addition the question of hepatic dysfunction was investigated in 48 schizophrenic patients using the Cephalin-Cholesterol Flocculation Test. The results of this investigation were essentially negative.

The present paper describes a chromatographic study of urine samples from 40 schizophrenic and 10 normal subjects. The object was to investigate the possibility of differences in the type of indoles excreted.

### EXPERIMENTAL OBSERVATIONS

In this part of the project it was planned to study a smaller series of schizophrenic patients, both from the clinical aspect and as regards the pattern of urinary excretion of indolic substances. It was anticipated that identification of the various indolic substances should be possible and that it might be possible to correlate any differences so found with clinical status or diagnostic grouping.

### MATERIAL

This consisted of 40 schizophrenic patients, 15 women and 25 men. The mean age was  $43.5 \pm 7.5$  years. Amongst the women the diagnostic categories were represented thus: Catatonic 2, Hebephrenic 7, Paranoid 6. Amongst the men there were 8 Catatonic, 6 Paranoid, and 11 Hebephrenic patients. It will be appreciated that these categories are primarily descriptive. Many patients over a period of years show a variety of symptoms which would strictly entitle them to placement in other diagnostic categories. For the purposes of this study the paranoid subgroup may be defined as an illness in which ideas of persecution with or without ideas of grandeur are prominent and persistent. Catatonic schizophrenia similarly means an illness in which alternations between stupor and impulsive excitement have been prominent and in which abnormalities in the motor sphere (i.e. gait and posture) have been noted. Hebephrenia means an illness in which blunting and incongruity of affect, hallucinosis and a rather rapid deterioration of the personality are prominent features.

Most of these patients had been in hospital a long time and there was no reasonable doubt about the diagnosis. However, they were all interviewed by

\* Based on work already submitted for the Degree of M.D. at the University of St. Andrews.

the author personally, the ward sister kindly supplied information about them, and the case notes were inspected. The mean length of illness for the whole group was  $17.2 \pm 7.6$  years. In addition ten normal subjects were studied (5 male, 5 female), the mean age being  $26.3 \pm 8.4$  years.

### METHODS

Once again "night urine" samples were examined. A concentration procedure based on that described by Dalglish (1955) was employed. (1) De-activated charcoal was prepared by adding slowly, with stirring, 100 g. of activated charcoal to a solution of 8 g. of stearic acid in 500 ml. of ethanol. The mixture was stirred for 60 minutes, was diluted with 5 litres of water and the charcoal was then collected on a Buchner funnel. The charcoal was then washed with more water and air-dried. (2) Fifty ml. of urine was adjusted to approximately pH 4 with acetic acid and was then shaken with 1 g. of de-activated charcoal. The mixture was then poured into a sintered glass funnel and the adsorbent collected on the sintered glass disc. It was then washed with further water to remove salts and aliphatic substances. Then 25 ml. of 7 per cent. aqueous phenol was added to the funnel and the eluate collected in a beaker. A further 10 ml. of distilled water was then passed over the charcoal and this eluate was also collected, giving a total volume of approximately 35 ml. (3) The eluate was evaporated under a water-pump vacuum and on a water-bath (the temperature was kept below  $80^{\circ}$  F.). Two further portions of 5 ml. of distilled water were added to the retort during the distillation to assist in the elimination of the phenol. The final volume lay between 5 and 15 ml. (4) One hundred microlites of the concentrate so prepared was then applied to the right-hand lower corner of sheets of Whatman No. 1 chromatography paper ( $33.5 \times 31.5$  cm.) and two-way ascending chromatograms were run (based on the method described by Jepson, 1955). The first solvent was Isopropanol-Ammonia and the second was Butanol-Acetic acid. The runs were performed in all-glass tanks (one for each solvent), the papers being held in position by steel clips attached to steel cross-wires (the tanks and fittings were supplied by Messrs. Shandon). The first run was allowed to proceed for about 16 hours, and the second run for about 10 hours. The papers were then dried in a fume-cupboard and subjected to location agents. (5) Two "papers" were prepared from each concentrate. The first paper was dipped in a ninhydrin-acetic solution (Jepson and Steven, 1953), dried and heated in an electric oven set at  $110^{\circ}$  F., for two minutes. The paper was examined under ultra-violet light provided by a Hanovia Chromatolite. Fluorescent spots were outlined in lead pencil, then this same paper was dipped in an Ehrlich solution, dried, and the coloured spots again outlined in pencil (broken line).

The second paper was examined initially under U.V.L., without any pre-treatment, and fluorescent spots were outlined in pencil (solid line), then this second paper was dipped in a sulphanilic acid reagent, dried and then the spots were outlined in pencil (broken line).

### REAGENTS USED

#### (a) *Ninhydrin-Acetic Acid*

Ninhydrin 0.2 g. made up with acetone to 90 ml. To this was added 10 ml. of glacial acetic acid. This reagent had to be made up freshly for each set of papers.



(b) *Ehrlich Reagent*

Ten g. of p-dimethylamino-benzaldehyde was dissolved in concentrated hydrochloric acid and made up to 100 ml. Ten ml. of this stock solution was diluted for use with 40 ml. of acetone.

(c) *Sulphanilic Acid Reagent*

Sulphanilic acid 4.5 g. was dissolved in 45 ml. of concentrated hydrochloric acid and made up with distilled water to 450 ml. (Stock solution A.). Sodium nitrite 25 mg. was dissolved in 500 ml. of distilled water (Stock solution B.). When required 10 ml. of A. was added to 10 ml. of B., and the mixture was allowed to stand for five minutes. To this was then added sodium carbonate 20 ml. of a 10 per cent. W/V aqueous solution. This latter was added cautiously as the mixture effervesces rather vigorously.

## IDENTIFICATION

Each "batch" of papers run consisted of two "urine samples" (two papers each) and one reference paper. On to the right-hand lower corner of this paper was "spotted" 10 microlites of a solution containing tryptophan, 5-hydroxy tryptamine, tryptamine, indolyl-acetic acid and 5-hydroxyindoleacetic acid (1 mg. per ml. of each substance). The reference paper was subjected to the ninhydrin-acetic acid and Ehrlich procedure.

In any sample in which a spot for indole-acetic acid was found the identity was confirmed by later running a third paper and treating it with an acid oxidizing reagent; a fresh saturated solution of potassium persulphate was prepared and to 1 drop of this was added 10 ml. of concentrated hydrochloric acid and 40 ml. of acetone.

It should be made clear that all these location reagents were used in shallow polythene trays as "dips".

Identification was effected by:

1. Comparison of Rf. values.
2. Comparison with reference paper.
3. Colour reactions with Ehrlich "dip".
4. Fluorescence under U.V.L., both in untreated papers and after treatment with ninhydrin-acetic acid.

5. Colour reactions with sulphanilic acid "dip".

6. Colour reactions in selected cases with acid oxidizing reagent.

In Table I below are shown the Rf. values obtained, using this technique, for the reference substances already listed. In Table II are shown the colour reactions for these reference substances.

TABLE I  
*Rf. Values for Reference Substances*

| Reference Substances          |    |    |    |    | Rf. Values $\times 100$ |                         |
|-------------------------------|----|----|----|----|-------------------------|-------------------------|
|                               |    |    |    |    | Isopropanol-<br>Ammonia | Butanol-<br>Acetic Acid |
| 5-hydroxy-indolyl-acetic acid | .. | .. | .. | .. | 15-20                   | 72-80                   |
| 5-hydroxy-tryptamine          | .. | .. | .. | .. | 54-60                   | 44-50                   |
| 3-indolyl-acetic acid         | .. | .. | .. | .. | 30-36                   | 85-95                   |
| Tryptamine                    | .. | .. | .. | .. | 74-84                   | 70-76                   |
| Tryptophan                    | .. | .. | .. | .. | 20-26                   | 44-52                   |

TABLE II  
Colour Reactions of Reference Substances

| Reference Substances | Fluorescence with U.V.L. | Fluorescence after Ninhydrin-acetic Acid | Ehrlich Reagent           | Sulphanilic Acid Reagent | Acid Oxidizing Reagent |
|----------------------|--------------------------|------------------------------------------|---------------------------|--------------------------|------------------------|
| 5 H.I.A.A.           | —                        | —                                        | purple-blue<br>—blue      | chocolate                | pink-purple            |
| 5 H.T.               | —                        | green-blue                               | blue-purple<br>—grey-blue | chocolate                | —                      |
| I.A.A.               | —                        | —                                        | pink-purple<br>—grey      | —                        | bright pink            |
| tryptamine           | —                        | green-blue                               | purple                    | —                        | —                      |
| tryptophan           | —                        | —                                        | purple                    | —                        | —                      |

## RESULTS

These are shown in Tables III, IV and V.

TABLE III  
Indole Substances Detected in Urine Concentrates from 40 Schizophrenic Patients

| Patient | 5 H.I.A.A. | I.A.A. | Indoxyl Sulphate | Tryptophan | Q.F.B. | "X" | Other Spots                                                 |
|---------|------------|--------|------------------|------------|--------|-----|-------------------------------------------------------------|
| J.D.    | .. X       | X      | X                | X          | X      | X   | B.G.E. Rf. 10-30                                            |
| H.R.    | .. X       | X      | X                | X          | X      | X   |                                                             |
| J.J.    | .. X       | X      | X                | X          | X      |     |                                                             |
| H.H.    | .. X       |        | X                |            |        |     |                                                             |
| M.S.    | ..         | X      | X                | X          |        |     | OE Spot at Rf. 15-45 and PRE Spot 50-90                     |
| J.R.    | ..         |        | X                | X          |        |     | PRE Spot at 52-90                                           |
| M.L.    | ..         |        |                  | X          |        |     | PRE Spot at 52-90                                           |
| I.G.    | ..         | X      | X                | X          | X      |     |                                                             |
| O.R.    | .. X       |        | X                | X          |        |     |                                                             |
| H.L.    | .. X       | X      | X                | X          |        | X   |                                                             |
| J.L.    | .. X       | X      | X                | X          | X      |     |                                                             |
| A.L.    | ..         |        | X                | X          | X      |     |                                                             |
| I.B.    | ..         | X      | X                |            |        |     |                                                             |
| M.G.    | ..         |        | X                | X          |        |     |                                                             |
| M.D.    | .. X       | X      | X                | X          | X      | X   | PRE Spot at Rf. 50-85                                       |
| M.C.    | .. X       | X      | X                | X          | X      | X   |                                                             |
| W.R.    | ..         |        | X                | X          |        |     |                                                             |
| W.W.    | .. X       | X      | X                | X          | X      |     | PRE Spot at Rf. 52-85                                       |
| J.D.    | .. X       | X      | X                | X          | X      |     |                                                             |
| T.McC.  | .. X       | X      | X                | X          | X      | X   |                                                             |
| H.McI.  | ..         | X      | X                | X          | X      | X   |                                                             |
| R.M.    | .. X       | X      | X                | X          | X      | X   |                                                             |
| T.R.    | .. X       | X      | X                | X          | X      |     |                                                             |
| N.R.    | .. X       |        | X                | X          | X      |     | Two OE Spots at Rf. 15-45 and 50-85 (both blue with U.V.L.) |
| W.B.    | .. X       | X      | X                | X          | X      | X   |                                                             |
| A.G.    | .. X       |        | X                | X          |        |     |                                                             |
| W.A.    | ..         | X      | X                | X          | X      |     |                                                             |
| N.K.    | .. X       | X      | X                | X          | X      |     |                                                             |
| J.B.    | .. X       | X      | X                | X          | X      |     |                                                             |
| J.R.    | ..         | X      | X                | X          | X      | X   |                                                             |
| H.S.T.  | .. X       | X      | X                | X          |        |     |                                                             |
| J.S.    | .. X       |        | X                | X          |        | X   |                                                             |
| W.R.    | ..         |        | X                | X          |        |     |                                                             |
| J.R.W.  | .. X       | X      | X                | X          |        |     |                                                             |
| R.C.    | .. X       | X      | X                | X          | X      |     |                                                             |

TABLE III (continued)

| Patient   | 5<br>H.I.A.A. | I.A.A. | Indoxyl<br>Sulphate | Trypto-<br>phan | Q.F.B. | "X" | Other Spots                      |
|-----------|---------------|--------|---------------------|-----------------|--------|-----|----------------------------------|
| D.McW. .. | X             | X      | X                   | X               |        |     | OE spot at Rf. 15-45—blue U.V.L. |
| R.O. ..   | X             |        | X                   | X               | X      | X   | OE spot at Rf. 15-45—blue U.V.L. |
| R.McC.M.  |               | X      | X                   | X               |        | X   |                                  |
| D.J. ..   | X             | X      | X                   | X               | X      |     |                                  |
| J.G. ..   |               |        | X                   | X               |        |     |                                  |

TABLE IV

*Indole Substances Detected in Urine Concentrates from 10 Normal Subjects*

| Subjects                                            | 5<br>H.I.A.A. | I.A.A. | Indoxyl<br>Sulphate | Trypto-<br>phan | Q.F.B. | "X" | Other<br>Spots |
|-----------------------------------------------------|---------------|--------|---------------------|-----------------|--------|-----|----------------|
| a .. ..                                             | X             | X      | X                   | X               | X      |     |                |
| b .. ..                                             | X             |        | X                   | X               |        |     |                |
| c .. ..                                             | X             | X      | X                   | X               |        | X   |                |
| d .. ..                                             | X             | X      | X                   | X               |        |     |                |
| e .. ..                                             | X             |        | X                   | X               | X      | X   |                |
| f .. ..                                             | X             | X      | X                   | X               |        |     |                |
| g .. ..                                             |               |        | X                   | X               |        |     |                |
| h .. ..                                             | X             | X      | X                   | X               |        |     |                |
| i .. ..                                             | X             |        | X                   | X               |        | X   |                |
| j .. ..                                             | X             |        | X                   | X               | X      |     |                |
| No. of subjects excreting various indole substances | 9             | 5      | 10                  | 10              | 3      | 3   |                |
| Per cent. incidence                                 | 90            | 50     | 100                 | 100             | 30     | 30  |                |

Spot Q.F.B. (quickly fading blue) occupied a position approximately that expected of serotonin (higher Rf. in IprA). However, the colour was different, it appeared earlier and the response to ninhydrin-acetic acid and U.V.L., was equivocal. The possible identity of this spot will be discussed later. The spot was termed Q.F.B., as it appeared to be identical with that recently reported by Riegelhaupt in schizophrenic urine (1958). Spot "X" (Rf. 22-70) gave pale purple, fading to blue-grey with Ehrlich. There was no response to the other location reagents. It was considered possibly to be indolylacetylglutamine. The spot found in a few urines at Rf. 15-45, giving a blue fluorescence (untreated) with U.V.L., and an orange reaction with Ehrlich's reagent was thought to be kynurenine.

The other spot at Rf. 50-90 (52-85) gave a purple-red reaction with Ehrlich's reagent but no fluorescence with U.V.L. This spot was thought to be  $\gamma$ -(3-indolyl)-butyric acid but this supposition was not confirmed by use of the acid oxidation reagent. This may be due to the fact that the colour with Ehrlich's reagent was pale and Ehrlich's reagent is very much more sensitive than the acid-oxidation reagent.

The numbers of schizophrenic subjects excreting these various indolic substances (excluding kynurenine and the other spot, supposed to be  $\gamma$ -(3-indolyl)-butyric acid) are shown in Table V.

TABLE V

*The Number of Patients Excreting Various Indolic Substances (40 Subjects)*

| Substances                               | H.I.A.A. | I.A.A. | T.   | I.  | Q.F.B. | "X"  |
|------------------------------------------|----------|--------|------|-----|--------|------|
| No. of patients excreting ..             | 26       | 27     | 39   | 40  | 23     | 13   |
| Per cent. of total No. of patients .. .. | 65.0     | 67.5   | 97.5 | 100 | 57.5   | 32.5 |
| Total No. of patients ..                 | 40       | 40     | 40   | 40  | 40     | 40   |



## DISCUSSION

The observations on the 40 schizophrenic subjects reveals that, apart from tryptophan and indoxyl sulphate which were more or less constant, the substances detected were 5 H.I.A.A. (65 per cent.) spots "Q.F.B." (57.5 per cent.) and "X" (32.5 per cent.). Haverback *et al.* (1956) using Udenfriend's quantitative method, found low normal values for the excretion of 5 H.I.A.A. in the schizophrenics they studied. Buscaino and Stefanachi (1958) found no significant difference as regards 5 H.I.A.A. between their schizophrenic and normal samples. These authors used a qualitative colour reaction described by Sjoerdsma *et al.* (1955), a chromatographic technique and also Udenfriend's quantitative method. They comment that in only 85 per cent. of cases in which the colour reaction had been positive was 5 H.I.A.A. detected in the chromatogram.

Leyton (1958) found that 20 per cent. of his schizophrenic subjects excreted less 5 H.I.A.A. than did the controls. Perhaps relevant to this is the fact that Lauer *et al.* (1958) found that their schizophrenic subjects did not respond to a "tryptophan load test" with increased excretion of 5 H.I.A.A. while all their control subjects showed a 100 per cent. increase in the excretion of this compound.

Spot "X" is believed by the author to be indole acetyl glutamine. This spot was detected in 32.5 per cent. of schizophrenic and 30 per cent. of normal samples. Leyton (1958) similarly found no significant difference in the excretion of this compound as between normals and schizophrenics. Buscaino and Stefanachi found indole acetyl glutamine less commonly in the samples from schizophrenic subjects.

Indole acetic acid (I.A.A.) was found in 27 schizophrenic urine samples (67.5 per cent.) as compared with 5 normal samples (50 per cent.) Buscaino and Stefanachi found I.A.A. slightly less frequently in their schizophrenic samples while Leyton found no significant difference. Ross (1913) originally reported that schizophrenics excreted an excess of I.A.A.

V. M. Buscaino (1952) quotes another Italian, Gullotta, as demonstrating in 1929 an excess of I.A.A., in schizophrenic urines. Similarly Sherwood (1958) is reported as having found an excess of I.A.A. in schizophrenia, phenylketonuria and terminal cancer cases. Out of interest the present author examined urine from five cases of carcinomatosis and one case of phenylketonuria. As expected the latter urine gave intense spots for I.A.A., and indolelactic acid (I.L.A.). However, I.A.A., was not detected in any of the cancer cases though one sample gave a very intense "Q.F.B." spot.

Spot "Q.F.B." appears to be identical with that reported by Riegelhaupt (1958) who so named it because it faded quickly. Rodnight and Aves (1958) report a spot with similar Rf. values and staining reactions. They named it "U 2", found that it was seen more commonly in schizophrenic urine and suggested that it was a skatole derivative. Buscaino and Stefanachi found a spot with similar Rf. values in isopropanol-ammonia and butanol acetic acid. The colour with Ehrlich's seems to have been similar to that found by Rodnight and Aves and by the present author.

Buscaino (1958b) suggests that, though he thinks "Q.F.B." may be 5-6 dimethoxy tryptamine, other workers doubt whether it is an indole at all. However, there seems to be no doubt that, whatever the identity of Q.F.B., may in fact be, it is excreted more commonly in schizophrenic urine.

The author inclines to the view that "Q.F.B." may represent more than one

substance as was found by Riegelhaupt (1958) who attempted to isolate it. If Q.F.B. does represent 5-6 dimethoxy tryptamine this finding may have some relevance. The general view of biochemists is that methoxy derivatives are the result of the activity of intestinal bacteria on dietary protein. Apparently there are exceptions to the rule; thus methoxy derivatives of oestrogen have been detected in human urine (Fotherby, 1958); Axelrod has detected methoxy-adrenaline in rat urine while Hoagland (1958) quotes Gaudette and Scott (1958) as detecting 3-methoxyadrenaline and 3-methoxy-4-hydroxy mandelic acid in rabbit urine after the administration of adrenaline labelled with  $^{14}\text{C}$ .

Whether the process of methoxylation occurs through bacterial action within the gut lumen or as a metabolic process within the body proper is to some extent an academic question at the present time. What is important is that four different laboratories have reported the more frequent detection, in schizophrenic as opposed to non-schizophrenic urine, of a substance variously called "Q.F.B." and "U 2". The author believes that the Rf. values and staining properties reported suggest that these different workers are in fact talking about the same substance. This finding may be due to dietary differences or other environmental artifacts of the sort noted by Horwitt (1956). This is a problem which clearly merits further research.

The only clinical correlation observed in this study was between the excretion of spot "Q.F.B." and the catatonic subgroup. There were ten catatonic subjects in all and seven of these were found to excrete Q.F.B. (70 per cent.). This incidence is higher than that for the whole group of 40 subjects (57.5 per cent.) but as the numbers are small the author does not feel justified in laying too much emphasis on this finding. No correlations, positive or negative, were found between indole excretion, age, length of illness or other diagnostic features.

#### SUMMARY

1. Concentrates were made from urine samples collected from 25 male and 15 female schizophrenic subjects, 10 normal subjects were also studied.

2. These concentrates were used in two-way ascending chromatograms and an attempt was made to identify the indoles detected.

3. One "abnormal" spot ("Q.F.B.") was found in 23 schizophrenic subjects and in 7 out of the 10 catatonic patients (70 per cent. incidence).

4. These results are discussed in relation to other reports on the excretion of indoles in schizophrenia.

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# PROGNOSTIC FACTORS IN THE ELECTROSHOCK TREATMENT OF DEPRESSIVE STATES

## I.—CLINICAL FEATURES FROM HISTORY AND EXAMINATION

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### INTRODUCTION

SINCE its introduction in 1938 electroshock therapy (E.C.T.) has become probably the most widely applied form of physical treatment in psychiatry, despite the fact that its method and site of action are still not precisely known. Numerous investigations have been undertaken to delineate more clearly the indications for its use; notwithstanding broad agreement as to its value in depressive states and some schizophrenic syndromes there is still a paucity of evidence on which firm criteria for the prediction of outcome to treatment can be based. Most prognostic studies appeared in the first decade following the introduction of E.C.T. and were based largely on empirical clinical observations during the course of routine psychiatric practice, whereas later investigations have included more intensive and precise researches into possible psychological, physiological, biochemical and pharmacological indices of capacity to respond to electroshock.

The relevant literature is both extensive and yet, on many points, inconclusive. Difficulties of objective assessment of clinical status, both qualitative and quantitative, are partly responsible: Kraepelinian diagnostic terms lack sufficient precision for the purpose of comparing results of treatment, and diagnostic criteria vary considerably among psychiatrists. Estimations of clinical change are also lacking in standard and comparable methods of assessment, and until comparatively recently there has been a lack of awareness of the importance of the initial planning of investigations to allow for the application of simple tests of statistical significance to the results and the avoidance of potential pitfalls, such as neglect of the time factor in assessing the results of treatment (Alexander, 1945).

Predictive value has been claimed, directly or indirectly, for a number of specific factors associated with the treatment of depressive states by E.C.T. These fall broadly into two groups, firstly the possible influence on outcome of clinical features derived from the history and examination, including age, physique and individual symptoms and signs, and secondly the use of more specific tests of various kinds.

In view of conflicting reports in the literature, and the desirability of validating other work in this field, the present investigation was undertaken.

### DESIGN OF THE INVESTIGATION

It was decided for various reasons to undertake an intensive and comprehensive study of a relatively small number of patients, without emphasis

on diagnostic categories, and to determine the relationship of various clinical and specific features to outcome with treatment by means of standard statistical methods. This was designed to detect and assess the influence of individual factors on short-term prognosis, with the possibility of immediate therapeutic guidance; the investigation by Hobson (1953) furnished a convenient starting-point. In this statistically significant associations were found between 20 clinical items and the immediate results of E.C.T. in 127 patients treated at the Maudsley Hospital, almost all with depression.

The most important requirements to avoid serious methodological errors appeared to be (a) the presence or absence of specific clinical features as such, within broad diagnostic limits, to avoid the ambiguity often attending diagnostic groupings; (b) an attempt to quantify depressive manifestations by means of a rating scale rather than by "global" assessments of clinical status; (c) the definition of clinical terms employed as far as possible; (d) the setting of a definite time interval for assessment of the results of treatment; and (e) the control of such variables as age, technique of treatment, etc. and overall design to allow for the application of standard statistical methods to the interpretation of results.

### *Selection of Patients*

Only women were selected for study, between the ages of 40–60 years. These limits were set to include the involutonal period, when many minor or atypical depressions occur, and to exclude older patients where organic factors might increasingly complicate matters. Only those women suffering from a depressive illness sufficiently severe to warrant the application of E.C.T. were included: a "depressive illness" was defined as a sustained primary mood disturbance, leading to subjective or objective inefficiency of mental activities experienced in a mood of sadness, and usually with a diffuse persistent lowering of interests and activity (Mayer-Gross, 1954; Partridge, 1954). E.C.T. was considered justified when symptoms were sufficiently severe to render the patient unfit for her normal occupation, or constituted a serious social handicap, or had led to an apparently genuine attempt at suicide. Patients with depressive symptoms in relation to organic syndromes, other psychoses, etc., were not included, nor were those who had had E.C.T. in the preceding 12 months. No attempt was made initially to place patients in closely-defined diagnostic categories, any otherwise suitable subject showing a sufficient degree of sustained primary mood disturbance being included.

Fifty-four patients were initially investigated, and 50 included in the present study.

### *Clinical Examination and Assessment*

Routine physical examination was carried out on all patients to exclude gross physical disease, and in view of the later administration of methacholine, those with asthma or heart disease were excluded; essential hypertension without evidence of cerebral, cardiac, or renal involvement was not considered a contra-indication. The physical measurements necessary for the calculation of the Rees-Eysenck body index (female) were also made (Rees, 1950); stature, height to symphysis pubis, circumference of chest at xiphisternum midway between inspiration and expiration, and hip circumference at the level of the iliac crests.

Routine history-taking and mental examination were supplemented by particular attention to the various clinical items described by Hobson as being of prognostic significance, and by the quantification of the symptoms and signs of depression and anxiety by the use of an appropriate rating scale. This was derived from a gloss of various depressive symptoms, arranged in appropriate groupings to cover the following headings:

- Depressive mood, guilt feelings, suicidal features.
- Insomnia—early, middle and late.
- Diurnal variation of mood.
- Interference with work and activities.
- Degree of psycho-motor retardation.
- Agitation.
- Anxiety—psychic and somatic manifestations.
- Depersonalization, derealization, nihilistic ideas.
- Paranoid symptoms.
- Obsessive-compulsive symptoms.
- Hypochondriasis.
- Depressive somatic symptoms (e.g. backache, abdominal discomfort).
- Loss of weight.
- Degree of insight into illness.

The scale has been shown to have a high degree of reliability between observers (Hamilton, 1959); the one used in this study was a slightly modified version.

Features which could be assessed simply as "present" or "absent" were scored 2 or 0 appropriately, occasionally 1 when slight or doubtful: those of varying distribution such as depressive mood, anxiety, etc. were scored on a 5-point scale, from "0—absent" to "4—very severe".

Despite its imperfections the use of this scale allows a higher degree of accuracy than overall clinical judgment, as well as furnishing a quantitative expression of severity of symptoms capable of handling by simple statistical methods.

After clinical assessment and before treatment was begun, various other investigations were completed which included a psychological test, the response to injected methacholine and methedrine, and the sedation threshold to sodium amylobarbitone: these tests form the basis of a separate report.

### *Treatment and Follow-up*

Patients were in all cases treated by E.C.T. modified with thiopentone and suxamethonium chloride following atropine: twice-weekly treatments were usually given until it was felt that maximum benefit had been obtained or that nothing further was to be gained by continuing electroshock. No fixed course was used, and the average number of treatments in the series was between 7 and 8. Most patients were able to be discharged from hospital within 2–3 weeks at most following the cessation of E.C.T. All were in-patients.

Reassessment of clinical status, using the rating scale, was carried out personally on every patient at approximately 30 days after the last treatment, and again 2 months later, i.e. at 1 and 3 months after completion of treatment.

## RESULTS

### *Age*

Ages of the 50 patients ranged from 41–60 years (mean 51.1 years). The relationship between age and outcome with E.C.T. at one and three months



respectively was examined by calculation of the coefficient of correlation ( $r$ ), using age in years and the total symptom-scores derived from the rating scale.

At 1 month after treatment  $r = -0.298$  ( $P = 0.05$ )

3 months  $r = -0.118$  (not significant).

This negative correlation indicates a tendency for the older patient in the series to have a lower total symptom-score after treatment, i.e. to have a better short-term prognosis, and the reverse for the younger ones. This trend is not a very marked one, however, nor is it sustained at the 3-month interval. In a fairly small series of 50 cases it may be partly due to bias introduced in the initial selection of patients. There is a statistically non-significant correlation ( $r = 0.265$ ) between age and initial symptom-scores before treatment, however, which does not suggest a marked selection bias.

### *Physique*

The body-index regression equation for females (Rees), expressed in standard measure, was first converted into an equation in which raw measurements from the patients could be used directly; this was calculated from the means and standard deviations given by Rees (1950) in the original work. The resulting equation did not give a sufficiently wide discrimination between patients of different physique, so that the original regression equation was multiplied 15 times to increase its standard deviation accordingly. From this a further equation was obtained which proved satisfactory: an arbitrary figure of 100 was added to each index-figure in order to obviate negative numbers.

The final equation was:

B.I. (F) =  $3.59$  stature +  $3.77$  symphysis ht. -  $1.91$  chest circumf. -  $3.73$  hip circumf. -  $159.39$  (measurement in inches).

The index ranged between 19 and 151; the distribution is shown in Table I.

TABLE IA  
*Distribution of Body-Index (Female)*

| Body Index | 0-20 | 21-40 | 41-60 | 61-80 | 81-100 | 101-120 | 121-140 | 141-160 |
|------------|------|-------|-------|-------|--------|---------|---------|---------|
| Number ..  | 1    | 1     | 4     | 9     | 18     | 12      | 3       | 2       |

This is a normal distribution and provides no evidence to suggest that an undue proportion of patients of a particular physique have been included in the series.

The indices were then correlated with the symptom-scores at 1 and 3 months respectively, the results being:

TABLE IB  
Symptom-score  
1 month      Symptom-score  
3 months

|                       |        |        |                                        |
|-----------------------|--------|--------|----------------------------------------|
| Body-Index (F): $r =$ | +0.617 | +0.767 | (both significant at the 0.001% level) |
|-----------------------|--------|--------|----------------------------------------|

### *Previous Hysterectomy*

Of the 50 patients, 11 (22 per cent.) had had this operation, all except two in the three years preceding their depressive illness.

No significant differences in mean symptom-scores at 1 and 3 months after treatment, or in diagnostic category, were found between the women who had had a hysterectomy and those who had not.

### *Clinical Item Score*

In addition to the three clinical assessments on the rating-scale for depression, a scoring method devised by Hobson (1953), based on the presence or absence of various clinical items, was also used. These items had been found to be significantly associated with the immediate outcome with electro-shock. The definitions of the various items were those used by Hobson in his original paper, except that "sudden onset" was taken as deterioration to condition on admission within four weeks.

For each of the following allegedly *favourable* clinical features, a score of 1 was given if it was *absent*:

Sudden onset.

Good insight.

Obsessional traits in the previous personality.

Self-reproach (here taken as a score of 2 or more on the "guilt" rating).

Duration of illness of less than a year.

Pronounced retardation (taken as a score of more than 2 on the rating-scale).

For each of the following allegedly *unfavourable* features, a score of 1 was given if it was *present*:

Mild or moderate hypochondriasis (taken as a rating of less than 3).

Depersonalization.

Emotional lability.

Neurotic traits in childhood.

Neurotic traits in adult life.

Hysterical attitude towards symptoms.

Intelligence above average.

Fluctuating course since onset.

Ill-adjusted or hysterical previous personality.

Thus for each patient a clinical item score was made, furnishing a simple numerical assessment which could be compared with outcome: a high rating denoted a presumably poorer prognosis than a low one.

Ratings by this method ranged from 0-12; their distribution and the mean symptom-scores at 1 and 3 months after treatment for each rating are shown in Table II.

TABLE II

#### *Scoring on Clinical Items (Hobson) and Mean Symptom-Score After Treatment*

| Clinical Item Score ..            | 0   | 1    | 2   | 3   | 4   | 5   | 6   | 7    | 8   | 9    | 10   | 11   | 12   |
|-----------------------------------|-----|------|-----|-----|-----|-----|-----|------|-----|------|------|------|------|
| No. with each rating ..           | 1   | 4    | 7   | 4   | 3   | 10  | 3   | 3    | 7   | 4    | 2    | 1    | 1    |
| Mean Symptom Score at 1 month ..  | 1.0 | 2.75 | 3.3 | 1.2 | 4.6 | 5.3 | 7.3 | 6.0  | 8.0 | 8.0  | 9.2  | 13.0 | 10.0 |
| Mean Symptom Score at 3 months .. | 1.0 | 4.75 | 2.8 | 1.3 | 5.2 | 5.9 | 4.6 | 11.3 | 9.1 | 13.0 | 11.5 | 12.0 | 18.0 |

n=50.

The distribution is an uneven one, but this is not necessarily of much significance in a comparatively small series of 50 patients.

The mean symptom-score at one month after E.C.T. shows a remarkably consistent rise (apart from 3 minor exceptions) *pari passu* with the clinical item score, and this is reflected in a correlation of +0.727 between them (significant at the 0.001 per cent. level for 48 degrees of freedom).

A symptom-score at one month of less than 5 points may be regarded as an indication of a "good" result of treatment, and a score of over 6 as "moderately good" to "poor".

Table III shows the distribution of cases with these symptom-scores in relation to the item-scores.

TABLE III  
*Scoring of Clinical Items (Hobson) and Degree of Recovery*

n=50.

| Clinical Item Score (Hobson) | .. | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|------------------------------|----|---|---|---|---|---|---|---|---|---|---|----|----|----|
| Number of patients with:     |    |   |   |   |   |   |   |   |   |   |   |    |    |    |
| Symptom-score (1 month) 0-5  |    | 1 | 5 | 5 | 4 | 2 | 6 | 1 | 2 | 2 | 0 | 0  | 0  | 0  |
| Symptom-score (1 month) 6+   |    | 0 | 0 | 1 | 0 | 1 | 4 | 2 | 1 | 5 | 4 | 2  | 1  | 1  |

From this table, an item-score of 5.5 points may be taken as an index of a good degree of recovery with treatment. Using this criterion 11 cases are seen to be misclassified, or 22 per cent. of the total. This is in close accord with Hobson's own figure of 21 per cent. of his total of 127 patients who were similarly misclassified.

The close association between the clinical item scoring of Hobson and the symptom score is less marked at three months after treatment (Table IV), the correlation being +0.666 (significant at the 0.001 per cent. level).

The relationship between the various clinical assessments which were made, i.e. the rating-scale assessments before treatment, at one and three months after E.C.T., and the scores on clinical items (Hobson) are demonstrated in Table IV.

TABLE IV  
*Correlation Between Clinical Assessments*

|                              | Clinical<br>Item<br>Score | Initial<br>Symptom<br>Score | 1 Month<br>Symptom<br>Score | 3 Months<br>Symptom<br>Score |
|------------------------------|---------------------------|-----------------------------|-----------------------------|------------------------------|
| Clinical Item Score (Hobson) | 1.0                       | -0.498                      | 0.727                       | 0.666                        |
| Initial Symptom Score ..     | <u>-0.498</u>             | 1.0                         | -0.353                      | -0.318                       |
| 1 month Symptom Score ..     | 0.727                     | <u>-0.353</u>               | 1.0                         | 0.582                        |
| 3 months Symptom Score ..    | 0.666                     | <u>-0.318</u>               | 0.582                       | 1.0                          |

#### *Initial Assessment and Improvement*

The initial symptom-scores before treatment show a closely similar negative correlation between the re-assessments at one and three months after electroshock:  $r = -0.353$  and  $-0.318$  respectively (significant at the 2 per cent. and 5 per cent. levels respectively).

The 50 case histories and clinical records were carefully scrutinized, and the diagnosis of "psychotic" or "neurotic" depression made on the criteria laid down by Mayer-Gross (1954). Some difficulties were experienced in a number of cases, most of which could be satisfactorily resolved after discussion with experienced colleagues, and by taking into account the *predominating* clinical features. Three cases remained where no clear-cut diagnostic differentiation could be made. The "psychotic" group contained 20 patients and the "neurotic" group 27. The number in each diagnostic category was then compared with the clinical-item scores of Hobson (Table V).



TABLE V

*Diagnostic Groups and Clinical Item Scores*

| Clinical Item Score (Hobson) | 0 | 1 | 2 | 3 | 4 | 5  | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|------------------------------|---|---|---|---|---|----|---|---|---|---|----|----|----|
| "Psychotic" .. .. .          | 1 | 4 | 7 | 2 | 2 | 4  | 0 | 0 | 0 | 0 | 0  | 0  | 0  |
| "Neurotic" .. .. .           | 0 | 0 | 0 | 1 | 1 | 5  | 2 | 3 | 7 | 4 | 2  | 1  | 1  |
| Unclassified .. .. .         | 0 | 0 | 0 | 1 | 0 | 1  | 1 | 0 | 0 | 0 | 0  | 0  | 0  |
| Totals .. .. .               | 1 | 4 | 7 | 4 | 3 | 10 | 3 | 3 | 7 | 4 | 2  | 1  | 1  |

n=50.

This shows clearly a differentiation into two groups, with a fairly small degree of overlap.

## DISCUSSION

It is readily apparent that an investigation such as the present one has necessary limitations, and individual variations and the general complexities of the problem make it futile to expect that prognosis can be reduced to a matter of a few simple figures. To attempt to isolate specific items from the clinical picture presented by each individual patient is clearly to make artificial divisions and to ignore other possible factors in the total situation—the effects of individual and group inter-personal relationships, chance environmental influences and so on. Although many of these factors are operating at random and for the purposes of this study have been ignored, in a comparatively small series of 50 patients their influence cannot be completely dismissed, and it is emphasized that conclusions drawn from the results above are to be interpreted with due caution.

A full review of the relevant literature on the prognostic significance of various clinical features of depressive illnesses, both before and after the introduction of E.C.T., is of considerable interest but cannot be included here. The possible significance of the various findings calls for further mention, however.

Before the advent of electroshock treatment a number of studies on depressed patients stressed the adverse influence of increasing age on the outcome; Strecker *et al.* (1931), Anderson (1936) and Rennie (1942) all remarked on the generally poorer prognosis when the illness occurred after the age of 40. Since the introduction of E.C.T. there has been some evidence that this trend has been at least diminished, and this is confirmed in the present investigation. This tendency for older patients to have a better outcome a month after treatment is not sustained at the three-month interval, however, and the patients concerned were initially selected to exclude those suffering from the organic cerebral complications commoner in the older age group.

The value of morphological indices for prognosis has chiefly been investigated in schizophrenics, the initial impetus to these researches having been given by Kretschmer's observations. Most studies of differences in body-build, and their association with outcome have stressed the better prognosis for individuals of more pyknic than asthenic habitus, but a number of investigators have not found any significant relationship between physique and prognosis. Many reports have been based upon general impressions of the physique rather than actual measurements, and the technique of somatotyping (Sheldon, 1940) has made researches in this field more scientific. A simpler index of somatic morphology is that suggested by Rees (1950) and called the "body-index (female)" obtained by factor analysis of inter-correlations between 15 anthropometric variables from 200 female patients to produce a regression equation

based on 4 simple measurements. Rees found that leptomorphy classified on the basis of this index was associated with dysthymic traits of anxiety and depression in 400 female neurotics, but emphasized that the correlation between physique and psychological studies is probably too small for clinical use in diagnosis or prognosis. The correlations between the body-indices and symptom scores after treatment in the present study are surprisingly high, and on a small series of patients must be treated with reserve. The inference is clear, however, that in the depressed patients observed, those with a lower body-index (i.e. tending towards endomorphy or a pyknic physique) have a distinctly better outcome with E.C.T. than those of a more leptosomatic habitus, and the trend is enhanced three months after treatment. Gildea *et al.* (1936) observed in normal people that high serum lipoids (fatty acids and serum cholesterol) were found in conjunction with pyknic body-build and high energy output; low lipid levels were found in individuals of asthenic or leptosomatic build and low energy-output. Further studies (Gildea *et al.*, 1940; Gildea and Man, 1943) suggested that the triad of pyknic physique, uncomplicated symptoms of manic-depressive psychosis and high serum lipoids were evidence of a high capacity for recovery in their patients.

In view of conflicting statements as to the importance of such stress factors as physical illness or operations, particularly those involving the genito-urinary system (Malamud *et al.*, 1941), the incidence of women in this series who had had a hysterectomy (22 per cent.) is of interest. The precise nature and extent of the operation, removal of one or both ovaries, etc. was not known in the majority of cases, and it must be remembered that all the patients were between 41–60 years, the age range in which hysterectomy is most frequently performed; nor is it known what proportion of non-depressed women of this age have had the operation. Nevertheless the proportion found seems a large one, although it appears unlikely to carry any prognostic implications for treatment.

The scoring method using clinical items for predicting short-term response to E.C.T. appears to be of definite value. The statistically highly significant correlations found in the present series between clinical item-scores and symptom-scores after treatment ( $r=0.727$  and  $0.666$  at 1 and 3 months respectively) confirm Hobson's claim that the results of his original investigation "can be of practical assistance in the formulation, treatment, and prognosis by indicating the significance of certain features". The proportion of misclassifications using this scoring method is also confirmed at about one-fifth of the total. The initial symptom-scores (Table IV) show a similar trend, with correlations with symptom-scores at 1 and 3 months after electroshock of  $-0.353$  and  $-0.318$  (significant at the 2 per cent. and 5 per cent. levels respectively).

There is thus a clear tendency for those patients with high symptom-scores to begin with to respond rather better to treatment, and vice versa: this is the more so at one month afterwards than at three months. Two explanations for these findings are possible. Either the difference is a quantitative one, as Garmany (1958) and others believe, and the more severe depressives respond better to E.C.T. than milder ones, or there is a qualitative difference with a variety or group of varieties of depression which are characterized by a higher initial symptom-score and a good response to electroshock, and a variety showing the reverse features.

Examination of the relationship between initial assessments and the clinical item score of Hobson gives a correlation of  $-0.498$  (significant at

the 0.001 per cent. level). Thus there is an even clearer tendency for the higher initial symptom-scores to be accompanied by low clinical-item ratings and vice versa. To obtain a high score on the clinical-item assessment a fairly large number of neurotic features must be present: Hobson has commented on the high proportion of neurotic traits in his series. If the differences noted above were due merely to different degrees of intensity of depression, it seems unlikely that marked neurotic traits should be so much commoner in the less severely depressed. When the numbers with particular clinical-item scores are classified according to diagnostic category, the higher scores (5 and above) tend to cluster markedly in relation to the group of "neurotic" depression, and it is particularly noticeable that in the present series no patient with a clinical diagnosis of "psychotic" depression, 20 in all, had a clinical item score of more than 5 points, and only 7 out of 27 in the "neurotic" depressive category had a score of 5 or less, and of these only 2 with a score of 4 and 3 points respectively. The evidence here strongly suggests, although it by no means proves, that there may well be a qualitative difference, and that there is a variety of depression, characterized by lower initial symptom-scores for depression on the rating-scale, a higher incidence of neurotic features and thus a higher clinical-item score (Hobson), and a tendency to do less well with E.C.T. Similarly there is a variety, or group, in which the opposite features are found. These clearly correspond to "neurotic" or "reactive" and "psychotic" or "endogenous" depressions. (The terms "reactive" and "endogenous" to imply mutual exclusion and specificity are misleading, as a psychotic depression may well be "reactive" in some senses, and endogenous constitutional predisposition is present in many depressions regarded as "reactive".)

Argument over the question of differentiation of depressive states has waxed and waned for many years, and much of the debate has been admirably and succinctly reviewed by Partridge (1949). Following the now classical historical, clinical and prognostic surveys of "melancholia" by Lewis (1934, 1936), controversy diminished for a number of years, but has again become more topical, and in addition further doubts have been cast upon the concept of "involutional depression" as a clear-cut separate clinical entity (e.g. Mayer-Gross 1954b; Tait *et al.*, 1957). Further evidence favouring the "separatist school" has been reported in recent years, including observations on depressed patients subjected to prefrontal leucotomy (Elithorn, 1958), sedation-threshold studies (Shagass, 1956) and the reaction of depressives to intravenous methylamphetamine (Roberts, 1959). The results of the present investigation also point in the direction of there being at least two varieties of depressive illness.

#### SUMMARY

1. The importance and historical development of the search for reliable prognostic guides for the electroshock treatment of depressive states is briefly indicated.

2. The design of an investigation into alleged prognostic indices is described, using a rating scale of depressive symptoms and signs for the assessment of clinical status. Fifty female patients, aged 41-60, with primary depressive illnesses were investigated, their physique measured, and later treated by E.C.T. Re-assessments of clinical condition were made at 1 and 3 months after the completion of treatment, and the association between specific clinical factors and quantitative symptom-ratings examined statistically.

3. A significant relationship with response to electroshock was found between patient's age, physique and a clinical-item scale (Hobson) derived from the history and examination.

4. Certain of the results support the view that there are at least two clinically separate varieties of depressive illness.

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# PROGNOSTIC FACTORS IN THE ELECTRO-SHOCK TREATMENT OF DEPRESSIVE STATES

## II.—THE APPLICATION OF SPECIFIC TESTS

By

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### INTRODUCTION

DURING the past ten years varying degrees of prognostic value have been claimed, directly or indirectly, for a number of specific factors in connection with the treatment of depressive illnesses by E.C.T. These have included the blood pressure responses to adrenaline and methacholine (Funkenstein *et al.*, 1948, 1950); the "sedation threshold" to intravenous sodium amylobarbitone (Shagass, 1954; Shagass and Jones, 1958); EEG changes under thiopentone following electroshock (Roth, 1951; Roth *et al.*, 1957); and psychological tests based on items derived from the Minnesota Multiphasic Personality Inventory (Pearson, 1950; Feldman, 1957, 1958; Welsh, 1952). Other studies have been made on the prognostic value of adrenocortical activity (Faure *et al.*, 1957); serum calcium levels (Gour and Chaudhry, 1957); the "amytal test" (Kahn *et al.*, 1956); and the administration of methylamphetamine ("methedrine") (Rudolf, 1956). Some of the techniques employed appear too complicated or unreliable in their interpretation to be of any practical clinical value, although a few are of great theoretical value in the contributions to further knowledge of the rationale of E.C.T.

Doubts as to the value originally claimed for some of these alleged prognostic indices have been expressed, e.g. on the adrenaline-methocholine test (Sloane and Lewis, 1956); on the "sedation threshold" (Ackner and Pampiglione, 1958); and on the various M.M.P.I. measures (Pumroy and Kogan, 1958).

### METHOD

The tests administered formed part of a larger investigation, other aspects of which have been reported separately (Roberts, 1959); the same patient population of 50 women, aged 40–60 years and suffering from a primary depressive illness, was used. Before E.C.T. was begun, a modified version of the adrenaline-methacholine test (Funkenstein) was given, the sedation threshold to sodium amylobarbitone estimated, and the effects of an intravenous injection of methylamphetamine ("methedrine") noted. A psychological test derived from the M.M.P.I., the Feldman "Ps Scale", was also given.

#### *Methacholine Test*

A modified form of this test of autonomic function was employed, using the methacholine portion only: the technical difficulties of obtaining reliable systolic B.P. readings every  $\frac{1}{4}$  minute in certain agitated depressives, together

with the frequent production of very unpleasant anxiety symptoms, led to this modification. Initial difficulties in a short trial series arose when a solution of methacholine chloride prepared by a drug firm was employed; B.P. responses were very variable even in the same patient, and several showed little or no reaction. A supply of the drug in powder form was obtained from the U.S.A. and an aqueous solution freshly prepared for each patient, with much more positive results.

The technique for the test finally adopted was based on that used by Sloane and Lewis (1957).

In the morning, under fasting conditions, the systolic B.P. was taken after the patient had been recumbent for at least 30 minutes. Readings were then taken for at least 5 minutes at  $\frac{1}{2}$ -1 minute intervals until 5 consecutive readings within 8 mm. Hg were obtained, their average being taken as the "basal B.P.". All readings were personally made and recorded. Ten mg. of freshly-prepared aqueous methacholine chloride solution in 1 c.c. was then injected intramuscularly; the systolic B.P. was recorded every  $\frac{1}{2}$  minute for 7 minutes, then every minute for 5 minutes, and then every 2 minutes until a total of 25 minutes had elapsed or the B.P. returned to the "basal" level and remained there for at least 5 minutes.

No particular difficulties were encountered using this technique; initially the information from each patient was transcribed on to 1 mm. square graph paper. Graphs were examined individually and sorted into groups on the basis of the following criteria (Gellhorn, 1953):

*Group I*—Cases with an initial fall of systolic B.P. to methacholine followed by a fairly rapid return to basal level and a marked secondary rise subsequently (Funkenstein's Groups I, IV, as far as methacholine responses only are concerned). "Increased central sympathetic reactivity" (Gellhorn).

*Group II*—Cases with an initial fall—small, moderate or marked—with re-attainment of basal pressure within 25 minutes, often within 8-12 minutes (Funkenstein's Groups II and III). "Normal central sympathetic reactivity" (Gellhorn).

*Group III*—Cases with an initial fall—often of marked degree—with failure to return to basal level within 25 minutes (Funkenstein's Groups V, VI, VII). "Decreased central sympathetic reactivity" (Gellhorn).

The maximum fall of B.P. to methacholine, age and basal pressures were also noted and the relationships of these variables examined statistically.

Following this sorting, the mean total symptom scores at one and three months after treatment were calculated for each group and compared. In addition the correlations between the maximum B.P. fall to the drug observed and the symptom score at the one-month interval; between the maximum falls and the patients' ages; and between the time when B.P. homeostasis was re-established and the one-month symptom scores. The time for homeostasis to be attained was read from the graphs and taken as the time in minutes for the B.P. to return to the basal level, or within 4 mm. of it, and remain there for 3 consecutive minutes.

### *The Sedation Threshold*

Sedation threshold estimations to sodium amylobarbitone were then made, initially by the technique originally described by Shagass (1954).

With the patient lying down, and having had no drugs during the preceding



12 hours, a resting EEG recording was made using 4 frontal scalp electrodes. When this was satisfactory, an intravenous injection of sodium amylobarbitone solution, equivalent to 0.5 mg. of the drug per kilo of body weight in each 1 ml., was given. Every 40 seconds 1 ml. was injected at an appropriate signal from an assistant with a stop watch, a mark being made on the record simultaneously. At a second signal 25 seconds after each injection the patient was asked to repeat such phrases as "5-6-7", "British Constitution", etc., in order to detect the onset of speech slurring. When this was first noted the record was again marked, and the injections usually continued for a further 2 or 3 intervals of 40 seconds subsequently. From the EEG records, sample periods of 2 seconds duration were taken from periods of 15 seconds before and 10 seconds after each injection point where 15-30 cycles per second activity appeared maximal. Using a finely engraved ruler (unfortunately no frequency analyser was available) fast activity waves were measured and their mean amplitude for each injection period calculated. The information thus obtained was then plotted on graph paper, the clinically observed slur points also being marked. The general trend of the results obtained from 20 consecutive patients was in accordance with Shagass's observations, the frontal fast activity being at a minimum to begin with and gradually increasing in amplitude as the amount of drug in circulation increased. Although an S-shaped curve was apparent in some cases, in most there were a number of "inflexion-points", even sharp dips in the graph rather than a plateau; sometimes several could be observed in a single plotting. Where a dip or flattening of gradient occurred within 80 seconds of the clinical slur-point the sedation threshold as defined by Shagass could be assessed, but in some cases no appropriate amplitude change was noted within these limits. Accurate localization of the threshold by EEG changes alone was not possible, and it was found necessary to use the clinical slur-point as well in order to decide which EEG inflexion-point should be used.

In view of these findings, together with the extremely laborious and time-consuming hand measurements necessary, it was decided to omit the EEG recordings and to use the clinical slur-point alone as an approximate index of the sedation threshold. It was appreciated that this might well detract from the accuracy of the estimations, particularly as the slurring of speech tended to be manifested a little later than the nearest EEG inflexion point in some records. A further possible source of error was the difficulty, also noted by Ackner and Pampiglione (1958) and Thorpe and Barker (1957), of deciding on the actual onset of slurring in some patients. Despite these objections it was felt that at least it should be possible to obtain sufficient information as to the potential predictive value of the procedure in order to determine the advisability or not of further studies.

The "thresholds" obtained for each patient in this way, and expressed in terms of mg. sodium amylobarbitone per kilo body weight were then correlated with symptom scores at 1 and 3 months, and the clinical item scores. Comparison of the threshold between the various diagnostic categories was also made.

### *Response to Methylamphetamine*

Usually later on the same day as the methacholine test, the patient was given 15 mg. methylamphetamine intravenously. The dose was chosen after considerable experience with this drug in a variety of conditions, this amount being insufficient in most cases to cause marked disturbances of behaviour, yet sufficient to have a clear effect upon mood and symptoms.

The general effects upon behaviour, mood and symptoms were closely observed over the subsequent 2-3 hours, and it was found that these fell roughly into two fairly distinct categories, depending upon whether the patient's mood and symptoms were changed in the direction of normality, or the reverse. With a number of patients the commonly observed initial phase of weeping, pressure of talk and emotional lability quickly settled into a more sustained period of general uplift of mood and feeling of greater well-being, and these reactions were classified under the "return to normality" heading. Others showed an immediate, or almost immediate, intensification of symptoms, particularly a worsening of any agitation present, often together with a deepening of the depressive affect, increased self-deprecation and so on.

The response was classified as one which brought the patient nearer to her normal self by reduction of symptoms—an "N" response, or one which intensified symptoms—an "I" response. Where more than very temporary fluctuations of mood, etc., occurred, the predominant reaction over the succeeding 2-3 hours was used as the criterion for classification.

In two patients a different reaction to the drug occurred, manifested by a mild degree of prostration, occasional vomiting, complaints of headache and trembling, and accompanied by a markedly hysterical attitude to these drug-induced symptoms. Both patients had clear evidence of hysterical traits in their previous personality.

### *The Feldman "Ps" Scale*

Before starting treatment, the patient was asked to sort the relevant 52 items of the M.M.P.I., which go to make up the scale, into the appropriate group of "true", "false" or "don't know", with instructions to keep the number in the latter category as few as possible. The cards were then checked against Feldman's groupings and a total "prognostic score" derived on the basis of 1 point for each item answered in a prognostically unfavourable direction.

Considerable difficulties were encountered in the use of this procedure, the chief one being the inability or unwillingness of some patients to attempt it. This was usually due to agitation, retardation or indecisiveness, and in a number of cases it proved quite impossible to obtain a completed series of sortings: in other cases the test was finished only with persuasion from doctor or nurse, and in some it was obvious that the results were unreliable because of inattention, poor concentration and the general inability of the depressed patient to persist at the task. Even before the results could be assessed the value of this test (assuming a validity for it which is by no means certain) was clearly jeopardized by these factors. A further source of difficulty was the tendency of some patients to include up to 10 or 12 items in the "don't know" category, which could not be scored.

## RESULTS

### *B.P. Response to Methacholine*

The accompanying table shows the mean symptom scores at one and three months respectively for each group of B.P. response to the drug.

Funkenstein treated cases with a resting B.P. of over 140 mm. separately: those in whom homeostasis was re-attained within the observation period were reported to have a worse response to treatment than those in whom the drug-induced hypotension persisted.

TABLE I

*Methacholine Response Groupings and Mean Symptom-Score at 1 and 3 Months*

| Methacholine Response |      |    |    |    | Mean<br>Symptom-Score<br>at 1 Month | Mean<br>Symptom-Score<br>at 3 Months |
|-----------------------|------|----|----|----|-------------------------------------|--------------------------------------|
| Group I               | (4)  | .. | .. | .. | 5.5                                 | 8.7                                  |
| Group II              | (26) | .. | .. | .. | 6.1                                 | 7.2                                  |
| Group III             | (20) | .. | .. | .. | 5.4                                 | 5.5                                  |

The present series of 50 patients included 13 in whom the basal B.P. was over 140 mm. These were subdivided into two further groups on the criterion of return to basal levels: Group A where homeostasis was reached within 25 minutes, and Group B where hypotension persisted.

*Group A*—4 cases. Mean symptom-score at one month=7.1 points.

*Group B*—9 cases. Mean symptom-score at one month=6.0 points.

Although there is a slight tendency for the Group A patients to respond less well to electroshock, the trend is very small and not significant in view of the small numbers involved.

Basal pressures and age were found to have a correlation of 0.517 (significant at the 0.001 per cent. level).

#### *Maximum B.P. Fall*

This was next examined in relation to outcome. The maximum fall was calculated from the "basal" reading to the lowest reading noted at any time during the test (usually within the first  $2\frac{1}{2}$  minutes).

Correlation ( $r$ ) between maximum fall and one-month symptom-score = -0.572. (This is significant (d.f.=48) at the 0.001 per cent. level.)

Maximum falls were also found to correlate highly with basal pressures ( $r=0.700$ ) and moderately highly with age ( $r=0.488$ ). The relationship of these variables is shown in Table II.

TABLE II

*Methacholine Response Variables, Outcome and Correlations*

|                       | Age    | Basal<br>Blood<br>Pressure | Maximum<br>Fall | Symptom-<br>Score<br>1 Month |
|-----------------------|--------|----------------------------|-----------------|------------------------------|
| Age                   | 1.0    | 0.517*                     | 0.488*          | -0.298                       |
| Basal blood pressure  | 0.517* | 1.0                        | 0.700*          | -0.168                       |
| Maximum fall          | 0.488* | 0.700*                     | 1.0             | -0.527                       |
| Symptom-Score 1 month | -0.298 | -0.168                     | -0.572          | 1.0                          |

\* Significant at the 0.001 per cent. level.

#### *Time of Homeostasis*

Four patients (Group I) showing a pronounced secondary rise were excluded from consideration.

Correlation ( $r$ ) between time of homeostasis and one-month symptom-score (46 cases) = -0.358. (This is significant at the 2 per cent. level.)

#### *Diagnostic Categories*

A comparison of the methacholine response groups and clinical diagnostic category is made in Table III.



TABLE III

*Methacholine Response and Clinical Diagnostic Groups*

| Methacholine Responses |    |    |    | "Neurotic" | "Psychotic" | Unclassified |
|------------------------|----|----|----|------------|-------------|--------------|
| Group I                | .. | .. | .. | 3          | 1           | 0            |
| Group II               | .. | .. | .. | 13         | 10          | 1            |
| Group III              | .. | .. | .. | 11         | 9           | 2            |
| Totals (n=50)          |    |    |    | 27         | 20          | 3            |

An incidental clinical observation of interest was that in all four cases of Group I (after-rise to methacholine) a tendency to develop marked post-E.C.T. anxiety was observed, which in two cases took several weeks to subside.

*The Sedation Threshold*

The distribution of the sedation threshold to sodium amytal, assessed in the majority of cases by the onset of slurring of speech, was as follows:

TABLE IV

*Distribution of Sedation Thresholds*

| Threshold (mg./Kilo)       | .. | 2.5-<br>3.4 | 3.5-<br>4.4 | 4.5-<br>5.4 | 5.5-<br>6.4 | 6.5-<br>7.4 | 7.5-<br>8.4 | 8.5-<br>9.4 |
|----------------------------|----|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| No. of patients (total=50) | .. | 6           | 7           | 11          | 12          | 8           | 5           | 1           |

This table shows a continuous distribution without any clear tendency to clustering which would suggest two or more separate groupings for the threshold.

The association between the threshold and the various symptom and clinical item scores is shown in Table V.

TABLE V

*Correlations Between Sedation Threshold and Symptom and Item Scores*

|                              | Sedation<br>Threshold | Symptom<br>Score<br>1 Month | Symptom<br>Score<br>3 Months | Clinical<br>Item<br>Score |
|------------------------------|-----------------------|-----------------------------|------------------------------|---------------------------|
| Sedation threshold (mg./K.)  | 1.0                   | + .491                      | + .424                       | - .556                    |
| Symptom score at 1 month ..  | + .491                | 1.0                         | + .582                       | + .727                    |
| Symptom score at 3 months    | + .424                | + .582                      | 1.0                          | + .666                    |
| Clinical Item Score (Hobson) | - .556                | + .727                      | + .666                       | 1.0                       |

Comparison of sedation thresholds with diagnostic category gives the following information:

|                            |   |               |
|----------------------------|---|---------------|
| "Neurotic" depressions     | = | 27 cases      |
| Mean sedation threshold    | = | 5.4 mg./kilo. |
| "Psychotic" depressions    | = | 20 cases.     |
| Mean sedation threshold    | = | 5.1 mg./kilo. |
| "Unclassified" depressions | = | 3 cases.      |
| Mean sedation threshold    | = | 6.0 mg./kilo. |

There is obviously no significant difference between the mean thresholds for the two main groups, and a "t" test is unnecessary. The numbers in the third group are too small for valid conclusions to be drawn.

*Methedrine Response*

These were recorded as "N" or "I" response, depending on whether the patient felt either more normal or her symptoms were intensified. Two other cases were excluded from general consideration as their responses were clearly atypical: because of the smallness of this particular sample, it was not felt that any valid conclusions could be drawn from their separate consideration.

The mean initial symptom-scores for the two main groups, together with the mean symptom-scores at one and three months respectively, are shown in the accompanying table.

TABLE VI  
*Methedrine Responses and Mean Symptom-Scores*

|                   |    | Initial<br>Symptom-Score | Mean<br>Symptom-Score<br>1 Month | Mean<br>Symptom-Score<br>3 Months |
|-------------------|----|--------------------------|----------------------------------|-----------------------------------|
| "N" Response (31) | .. | 22.2                     | 6.9                              | 7.4                               |
| "I" Response (17) | .. | 31.5                     | 6.6                              | 3.9                               |

n=48.

At one month there is no meaningful difference in symptom-score between the two groups, but the "N" response group has a considerably higher symptom-score at three months after treatment, i.e. are less well after that interval. This difference is statistically significant at the 1 per cent. level (F ratio=7.19).

The relationships of the methedrine responses to clinical diagnostic categories are indicated in Table VII.

TABLE VII  
*Methedrine Responses and Diagnostic Category*

| Diagnostic Category |    | "Neurotic" | "Psychotic" | Unclassified | Totals |
|---------------------|----|------------|-------------|--------------|--------|
| "N" Response        | .. | 25         | 3           | 3            | 31     |
| "I" Response        | .. | 1          | 16          | 0            | 17     |
| Atypical            | .. | 2          | 0           | 0            | 2      |
| Totals              | .. | 28         | 19          | 3            | 50     |

*"Ps" Scale*

The difficulties attending the use of this test have already been commented on, and 9 patients did not complete it for various reasons. Of the 41 patients who sorted all the cards, the results were of doubtful value in 11 because of the high number of "don't know" responses which could not be scored.

The scores obtained from the 41 subjects were correlated with the symptom scores at one and three months after treatment, with the following result:

1 month rating      3 month rating

"Ps" Score      0.236      0.225

In neither case is  $r$  significant at even the 10 per cent. level.

## DISCUSSION

*The Methacholine Response*

There is now a fairly large literature on various aspects of the adrenaline-methacholine tests of autonomic function, and many of the published reports

claim considerable value for it in relation to outcome with electroshock therapy. (Funkenstein, 1952; Alexander, 1955; Brothers and Bennett, 1954; Blumberg *et al.*, 1956; Stemmerman and Owen, 1957). The test has been applied in a wide variety of psychiatric conditions, and although it appears to cut across diagnostic categories to some extent, Sloane *et al.* (1957b) found some promise for diagnosis in multiple correlations from the B.P. response curves. These workers, however, reported that in their series of 111 patients those with B.P. responses to methacholine most similar to those of normal controls showed the best outcome to E.C.T., and marked hypotensive reaction to the drug was not found to be significantly associated with good prognosis. These findings were the opposite of previous reports, except for that of Montagu and Davies (1955) who found the test of no prognostic help in the treatment of anxiety states by electro-stimulation. Other factors apparently influencing the test have been reported as duration of stay in hospital, particularly affecting schizophrenics (Geocaris and Kooiker, 1956); the patient's age (Blumberg *et al.*, 1956; Nelson and Gellhorn, 1957); the height of the resting or "basal" B.P. (Funkenstein *et al.*, 1952); and possibly the status, etc. of the person administering the test (Maas, 1958). A survey of the relevant work suggests that disturbances of autonomic function, as measured by methacholine B.P. responses, appear considerably more frequently in psychiatric patients, and that there is a relationship between these responses and outcome to E.C.T., the degree of this association being at present unclear.

The comparison of mean symptom-scores, as assessed on the rating scale, for the 3 main groups of B.P. response curves to methacholine in the present series shows no significant difference at one month after treatment. At the 3-month interval there is some tendency for those in Group I (after-rise) and Group II (homeostasis within 25 minutes) to have worsened slightly. This is the more marked in Group I, but as only 4 patients were included in this category no valid conclusion is possible. The mean symptom-scores for the Group III (prolonged hypotension) remained similar throughout, and the difference between the means for Groups II and III is not significant ( $F$  ratio = 1.19).

Similarly a basal B.P. estimation of over 140 mm. Hg was not found to be significantly related to outcome 1 month after treatment.

The moderately high correlations found between age and basal B.P. ( $r=0.517$ ), age and maximum B.P. fall ( $r=0.488$ ), and a higher correlation between basal B.P. and maximum fall ( $r=0.700$ ) are in keeping with previous findings by various workers. The relationships between age, basal B.P. and maximum fall and the symptom-scores one month after treatment were less marked, only that with maximum fall approaching a moderately high degree ( $r=-0.572$ ). This finding tends to confirm Funkenstein's assertion that a marked drop in B.P. to methacholine is a favourable prognostic sign, but in view of other variables found to be related to the fall in pressure, notably age and the basal pressure, this finding is almost certainly not merely a reflection of the action of the drug only. The time for homeostasis to be attained is related to a minor extent with outcome (at 1 month  $r=-0.358$ ) but again the trend is not sufficiently well-marked to be of practical prognostic help. No clear relationship between the methacholine response pattern and diagnostic category was found.

As far as the series of patients under investigation was concerned, therefore, no clear confirmatory evidence as to the prognostic claims made for B.P. responses to methacholine was forthcoming, only the variable of maximum



observed fall in pressure having even a moderately high association with outcome; even this was not sufficient to be of unequivocal clinical value.

### *The Sedation Threshold*

A number of papers have now been published on this theme (Shagass, 1954, 1956, 1957; Shagass and Naiman, 1955, 1956; Shagass and Jones, 1958; Shagass *et al.*, 1956, 1957). Claims have been made for a 95 per cent accuracy in differentiation between "neurotic" and "psychotic" depression (Shagass *et al.*, 1956) and a predictive value for outcome to electroshock based on this alleged diagnostic efficacy.

Examination of the data from the 50 depressives shows a normal continuous distribution, with a fairly well-marked relationship between the sedation threshold (using clinical slurring alone) and symptom-scores ( $r=0.491$  and  $0.424$  at one and three months respectively), with a slight falling-off in the strength of the association at the 3-month interval. This tendency for a higher threshold to accompany a higher symptom-score after treatment is in line with Shagass's findings, though the trend is not as clear as his work has suggested. He has claimed that a threshold over a critical value of about 4 mg. sodium amylobarbitone/kilo body-weight will differentiate the two varieties of depression; clinical item-scores, which have been shown to contain more neurotic traits (Hobson, 1953), would thus be expected to show a fairly high positive correlation with the sedation-threshold to be in line with this theory. In this series the reverse is found, with a significant negative correlation ( $r=-0.556$ ), evidence of a tendency for higher thresholds to be associated with lower clinical item scores. The reason for this finding is not clear.

Comparison of mean thresholds in the diagnostic groupings shows no clear differences, and this finding does not confirm the reports by Shagass and his colleagues on the diagnostic, and hence prognostic, aspects of the test in depression. The present results are closely in accord with those of Ackner and Pampiglione (1958) however, who found mean thresholds of 6 mg./kilo for a group of patients diagnosed as "anxiety and neurotic depression" as well as a group of hysterics. Three other diagnostic groups (obsessional states, mixed neuroses and endogenous depression) had a similar mean threshold of 5 mg./kilo, and their report failed to confirm the reported experimental link with personality theory (Eysenck, 1955). It is appreciated that the method used in this present study, based on speech changes alone, is open to criticism.

### *Methylamphetamine*

The use of this compound for diagnostic purposes in psychiatric practice has been described by Simon and Taube (1946). Levine *et al.* (1948) reported its effects in producing relaxation, euphoria, increased alertness and relief of tension in neurotic patients, but intensification of delusions and florid phantasies, increased psychomotor activity and emotional discharge in a group of psychotics. Rudolf (1949) has urged the use of the drug in the treatment of depressive states, and compared (1956) the results of treatment with methylamphetamine or E.C.T. reported by various authors. Since the comparisons were drawn from a variety of sources, sometimes with admittedly incomplete details of diagnosis or outcome, such a summation of results is not very reliable. There was some evidence to show, however, that a higher proportion of "involutional depressives" and "depressives with anxiety" showed a better response to E.C.T. than to the drug, whilst "reactive depressives" did better

with methylamphetamine. Some evidence has accrued regarding its mode and site of action: Liddell and Weil-Malherbe (1953) reported increased blood adrenaline levels after its administration. Rothballer (1957), after experiments on anaesthetized cats with coagulation lesions in the mid-reticular system, has postulated that methylamphetamine produces its stimulant action on the C.N.S. by a sensitizing effect upon an adrenergic (adrenaline-sensitive) component of the reticular activating system.

The effects noted in the patients under investigation, whilst the observations made were superficial and to some extent subjective, were sufficiently striking to warrant mention. Though mean symptom-scores 1 month after treatment were similar in patients who showed either main type of response to methylamphetamine, at the 3-month interval there was a considerably higher symptom-score, i.e. less well, in the group whom the drug initially made more normal. This difference is statistically significant at the 1 per cent. level. When the drug responses on mood activity, etc. were grouped according to diagnostic category an even clearer difference was seen, 25 out of 28 "neurotic" depressions showing an amelioration of symptoms with the drug, and 16 out of 19 "psychotic" depressions showing an intensification of symptoms. The two atypical responses with hysterical features were seen in the "neurotic" group as might be supposed. These differences are hardly to be expected if the variation between clinical varieties of depressive illness was purely one of degree, and strongly support a qualitative difference. It is concluded that the response to intravenous methylamphetamine in this investigation has more application as a diagnostic aid, its prognostic value being of a relatively low order.

### *The Feldman "Ps" Scale*

There is no dearth of prognostic studies attempting to relate performance on various psychological tests and projective techniques to the eventual outcome of psychiatric disorders, though relatively few have been concerned with depressed patients and their response to E.C.T. A useful survey and critique of the field is that of Windle (1952) who found work in this field "discouragingly unorganized". The most promising technique appeared to be that of Feldman (1957) who selected 52 items from the M.M.P.I. by analysis of the records of patients improved or unimproved after shock treatment, and found high scores on this "Ps" Scale were significantly associated with unimprovement. This finding was not substantiated by Pumroy and Kogan (1958), and Feldman himself later (1958) modified both the scale and also the claims for its predictive value; it has been enlarged to 62 items and is considered only moderately valid as a prognostic guide.

In this investigation not only were considerable practical difficulties encountered in the administration and scoring of the Ps scale, but no significant correlations between score and outcome at 1 and 3 months after treatment were found in the data from the 41 patients completing the test.

### SUMMARY

1. The application of specific tests of alleged prognostic value to a group of 50 female depressives, subsequently given E.C.T., is described. These included the systolic B.P. response to injected methacholine, the "sedation threshold" to sodium amylobarbitone, the reaction to intravenous methylamphetamine, and a psychological test, the Feldman "Ps" Scale, derived from the M.M.P.I.

2. Difficulties found with the techniques and evaluation of the tests are described and the results discussed in relation to previous work and their significance.

3. With the B.P. response to methacholine only the maximum observed fall of pressure was found to have a moderately high correlation with outcome after E.C.T. This relationship was not sufficiently close for unequivocal prognostic guidance.

4. The sedation threshold to amylobarbitone (using speech-slurring alone) did not distinguish between "neurotic" and "psychotic" depression in this series. Correlations between the threshold and symptom-rating scores after treatment were too small for predictive purposes.

5. The overall clinical response to a 15 mg. dose of intravenous methylamphetamine ("methedrine") showed a clear tendency to separate patients into two groups closely related to diagnostic category, with lesser prognostic implications.

6. The "Ps" Scale (Feldman), derived from the M.M.P.I., had no significant relationship with outcome to treatment.

#### ACKNOWLEDGMENT

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# OBSERVATIONS ON THE PATHOLOGY OF INSIDIOUS DEMENTIA FOLLOWING HEAD INJURY

By

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HEAD injury, whether single as in an accident, or recurrent as in boxing, may on rare occasions be followed by a form of insidious dementia (Bowman and Blau, 1940). The post-mortem study of such long-standing cases however is seldom undertaken, and although various pathological processes may have been postulated during life they have rarely been looked for after death. The findings in the following case are therefore reported in some detail.

## CLINICAL HISTORY

A healthy married man with two grown-up children had for several years been running his own outdoor business. He worked hard, interviewing clients, making estimates, keeping the books and acting as a general supervisor. He was ambitious, he mixed well with people and was considered to be efficient and successful. His home life ran with equal smoothness, but possibly along the lines laid down by his wife. His parents, both in their eighties, were alive and well. He had one healthy brother, two years his junior, and one healthy son. His 29-year-old daughter has, since his death, had two psychotic episodes, each following the birth of her children.

In May 1949, at the age of 50, the patient was a passenger in a car when a collision occurred and he was knocked insensible. After removal to the casualty department of the local hospital, he was found to have regained consciousness but to be tremulous and shocked. A scalp laceration  $2\frac{1}{2}$  inches long over the left temple was sewn up, an abrasion on his nose was dressed, and bruising of the chest and legs was noted. "No severe injury" was thought to have occurred and he was sent home.

The following day the patient affirmed that he could remember nothing of the accident itself but that he had awakened to find himself pinned under the car. He had then again become unconscious, finally coming round in an ambulance.

From this time on the patient frequently saw his own doctor, partly because of his injuries but also because he found himself unable to concentrate or to do any work. He had begun to suffer from frequent headaches with a muddled feeling in his head, and occasional giddy attacks occurred (in one of which he fell and cut his nose badly). After three months his condition was no

better and he now complained of difficulty with his memory and at times of weakness of his legs. He was extremely worried by the state of his business, for he could not cope with the work. Much of his trouble however was at this time put down to uncertainty about the claim for damages which had been made after the accident.

During the following year little change was noted, but in view of the pending court action a number of expert opinions were sought. On both sides it was agreed that the patient had suffered "considerable organic damage" so that any conflict of views was confined to assessing the severity of its effects. The medical examiner for the defence contended that the damage was less than had been made out in this history. On the other hand, the medical expert for the plaintiff, who had seen the patient several times between September 1949 and January 1951, said after the latter date: "There has been no improvement and I even think he has deteriorated intellectually. He is irritable and unstable; he cannot plan ahead; his powers of concentration and of memory are both impaired, and the prognosis is very poor. The gross intellectual deterioration indicates, in my opinion, gross cerebral damage due to the head injury." At about the same time Dr. G. A. Foulds, Psychologist to Runwell Hospital, summarized his findings (based on an examination in January 1951) by saying: "The pattern of test results is characteristic of that seen in cases with cerebral damage and the deterioration is probably largely irreversible."

Two electro-encephalographic recordings had been taken, the first in October 1949, the second in January 1951. Both were reported on by Dr. S. L. Last as "abnormal, showing low alpha activity and diffuse low-voltage theta activity. There were no focal features."

In March 1951, about two years after the accident, the case was finally heard in the High Court and the patient was awarded a little under £8,000 damages, in respect of "personal injuries received while a passenger in a motor car which was involved in an accident with a taxi-cab".

For the next four years the patient remained at home, looked after by his wife and by his own doctor, whose occasional notes tersely summarized the downward course.

Early in 1954 Dr. G. A. Foulds saw the patient again and gave his opinion that further gross deterioration had taken place.

By the end of this year it was necessary to admit the patient to Runwell Hospital. He was now found to be severely demented, completely disorientated, and with little memory. His speech was slurred, there were both a coarse tremor and cog-wheel rigidity of his four limbs. The deep reflexes were exaggerated but equal on both sides. No ankle clonus was present; the plantar responses were flexor. Apart from a left spermatic varicocele, no other physical abnormalities were found. His ocular fundi were normal. His blood pressure was 180/105. A few days later he returned home for a further three months, but in April 1955 he finally had to be taken to Rochford General Hospital where he died one month later, at the age of 55.

#### POST-MORTEM EXAMINATION

A post-mortem examination was carried out by Dr. H. Williams, to whom we are grateful for this summary of his findings and for allowing us to study the brain: Wasted middle-aged man, with a healed scar  $1\frac{1}{2}$  inches long over the left temple. Death was attributed to basal broncho-pneumonia in a case of post-traumatic dementia. The heart (weight 220 grams) was small and atrophied;

no coronary or valvular disease was present. The right kidney was small, weighing only 50 grams, the left was normal, as were all other organs, apart from the brain.

No macroscopic abnormality of the skull or of the dura mater was found. After fixation of the sliced brain in 10 per cent. formalin the weight was 1,375 grams. The leptomeninges were moderately thickened over the convexity of both hemispheres and a slight degree of diffuse atrophy was present; the lateral ventricles were a little enlarged. The cerebral vessels appeared normal, and no localized lesion or evidence of past injury was found either in the hemispheres, the brain stem or the cerebellum.

### HISTOLOGICAL EXAMINATION

Representative blocks for nitrocellulose embedding were taken from the left frontal and left occipital lobes, through the left corpus striatum, and from both temporal lobes to include the hippocampal formations; from the mid-brain, pons and cerebellum. Staining methods included Nissl using cresyl violet, Heidenhain-Woelcke for myelin, Mallory's phosphotungstic acid haematoxylin, iron haematoxylin and van Gieson's counterstain, Holzer for astrocytes, Turnbull for iron, and Congo Red. Frozen sections of frontal, temporal and occipital areas, of the striatum and thalamus, and of the mid-brain, pons and medulla were impregnated with silver using von Braunmühl's method for senile changes. Penfield's method for microglia and an Hortega method for astrocytes were also used.

#### *Plaque Formation*

The formation of typical senile plaques was intense in all the cortical areas examined (Fig. 1). No particular variability from place to place was noted. The outer layers of the cortex were more affected than the deeper ones. An occasional plaque was present in the thalamus, the striatum and the tegmentum of the pons; none was seen in the pallidum, the mid-brain or the medulla.

#### *Alzheimer's neurofibrillary changes*

A very large number of nerve cells in all cortical areas were affected (Fig. 1). At sub-cortical levels the tangles were seen only in a few of the pigmented cells of the substantia nigra (Figs. 2, a and b), and of the locus caeruleus.

#### *Blood vessels*

In the occipital lobe many of the small pial arteries and their perforating intra-cortical branches were thickened, the middle coat often almost homogeneous and without nuclei. Elsewhere in the cortex such hyaline vascular changes were slight and only seldom seen.

The leptomeninges showed a moderate increase in fibrous tissue, particularly over the frontal convexity. Slight diffuse nerve cell loss with some pigment atrophy of those remaining was noticed at times in the cerebral cortex but these changes were never striking. No appreciable degree of myelin breakdown was found, but the radial myelinated fibres in the deeper layers of the cortex were often distorted or displaced by the plaque formation. Throughout the cortex a mild degree both of microglial and of astrocytic proliferation had taken place, the former chiefly in and around the senile plaques. A moderately



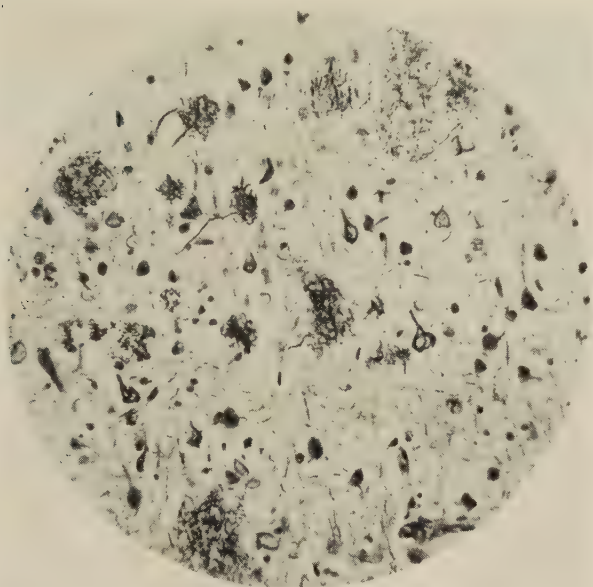
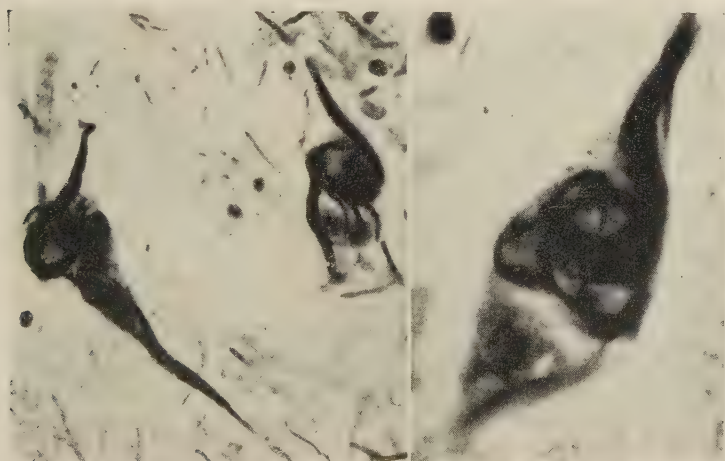


FIG. 1.—Silver impregnation (von Braunmühl's method) of cerebral cortex showing senile plaque formation and Alzheimer's neurofibrillary change.  $\times 230$ .



FIGS. 2a and 2b.—Silver impregnation of nerve cells in the substantia nigra to show the neurofibrillary tangles. Fig. 2a  $\times 460$ ; Fig. 2b  $\times 920$ .

dense but patchy sub-pial and sub-ependymal glial fibrosis was present throughout the brain.

The histological changes were those usually associated with cases of Alzheimer's disease or of senile dementia.

#### DISCUSSION

It is impossible to know whether this case is an example of Alzheimer's Disease in which an accident occurred at the very onset or whether it is a true

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instance of "post-traumatic dementia" in the sense that the clinical picture was the effect of the injury.

A very similar case was recorded by Claude and Cuel (1939). A woman of 50, deaf but with no past history of mental illness, was knocked down by a car and suffered "a brief loss of consciousness". During the following months she began to grow thin and to look older; previously cheerful, she became dull and apathetic. Within a year of the accident her memory and her sense of orientation noticeably deteriorated, and after another four years she was admitted to hospital completely demented, her condition being ascribed to "the effects of a head injury five years before". She died from pulmonary tuberculosis at the age of 57. At the post-mortem examination no evidence of past injury either to the brain or to the skull was found, but there was a slight degree of diffuse cerebral atrophy. The histological findings were those seen in Alzheimer's Disease.

In each of these cases there was never any doubt during life about the supreme importance of the head injury, and to dismiss out of hand its relation to the onset of the dementia would seem to be as uncritical as to accept it without reservation. In other words, the cases, while inconclusive in themselves, inevitably draw attention to a most interesting and largely unexplored pathological problem:

It is generally accepted that injury to the head may be followed at times by a deterioration in behaviour and in personality which in rare cases may progress insidiously to a state of advanced dementia. Since this dementia is of the type usually associated with the disintegration of cerebral tissue it may reasonably be postulated that cases of post-traumatic dementia would also be likely to show some form of demonstrable organic change.

There is however remarkably little known about the type of lesion, or perhaps more accurately the type of pathological process, that might be identified either after one or after repeated injury. What discussion there has been has mainly centred round the latter in relation to the medical aspects of boxing. Critchley (1957) in his review of 69 boxers with chronic neurological disease pointed out that the well-known condition of "punchdrunkenness" might be more accurately described as a "chronic progressive traumatic encephalopathy", since one of its most interesting features, especially from the pathological point of view, is the fact that it does not remit but that it steadily advances even though the boxer has long since retired.

Martland in 1928 had suggested that this might be explained by assuming that repeated injury produces multiple small haemorrhages throughout the brain which in time formed scars and led to cerebral atrophy. Kaplan and Browder (1954) however have more recently pointed out that there has so far been no direct pathological evidence to support this hypothesis, and the problem remains unsolved. Moreover an unusual paradox is implied by the theory, since the clinical picture would seem to get progressively worse during and even after the time in which the pathological lesions are presumed to have been gradually healing.

In fact the insidious nature of this clinical deterioration and the way in which it may progress long after the last injury would be in many ways better explained, not in terms of scarring, but by the development following trauma of some form of progressive degeneration of cerebral tissue.

It may not therefore be coincidence that the two cases of "dementia pugilistica" so far reported with full pathological details fit in with this latter hypothesis, and not with that of Martland.

Brandenburg and Hallervorden (1954) described and discussed in great detail the case of an amateur middle-weight boxing champion who fought for ten years, starting at the age of 18. During that time he was frequently knocked out. On retiring at 28 he was said to have become "a bit weak in the head" but it was at 38 that definite evidence of dementia was first established. Over the next 13 years he gradually deteriorated further until he died after a cerebral haemorrhage aged 51. In the last few years of his life, in addition to being severely demented, he had developed a Parkinsonian-like state. At the post-mortem examination no evidence of vascular disease or of past injury to the skull or brain was found, but a massive recent haemorrhage in the right frontal lobe was present. Microscopical examination revealed intense senile plaque formation with Alzheimer's neurofibrillary changes in many nerve cells and "amyloid" change ("drüsige Entartung") in the small vessels.

Brandenburg and Hallervorden considered this to be an example of post-traumatic dementia with Parkinsonism, and held the pathological changes to be the consequence of the repeated damage to the head. They pointed out that although the changes they described were those essentially associated with advancing age, there is nevertheless evidence that their development may be triggered off at a given time by the occurrence of a particular illness or injury.

Grahmann and Ule (1957) reported the clinical and pathological findings in the second recorded case. This patient had boxed for ten years, first as an amateur and then in the fair booths. He gave up at the age of 25 because of "weakness". He had occasional Jacksonian attacks from the age of 36 to 39; when 46 he was found to show severe mental deterioration, and he died two years later demented and with evidence of extra-pyramidal disease. An air encephalogram had been carried out a few days before death and at post-mortem examination there was widespread thrombosis of the cerebral veins with haemorrhagic infarction of the right frontal convexity of the brain. No evidence of earlier injury was found but the anterior horns of the lateral ventricles were moderately enlarged. The main histological lesion was that of Alzheimer's neurofibrillary change, scattered especially in the mid-brain and the metencephalon but also in the cortex and the diencephalon. No evidence of any type of vascular disease was found, nor were senile plaques identified.

Grahmann and Ule, after comparing their case with that of Brandenburg and Hallervorden, remarked that "the fundamental similarity of the morphological findings in these, the only two demented boxers so far to have been examined pathologically, is certainly no accident". They interpreted the findings in much the same way as Brandenburg and Hallervorden and pointed to the slowly progressive type of pathological process that was present in these cases. They noted that such a process would fit in with the clinical course of the condition more satisfactorily than one based essentially on the episodic destruction of tissue with scar formation.

It may be added that in our own material of the various senile and pre-senile dementias (which includes about forty cases of Alzheimer's Disease alone) a past history of major boxing has only twice been invoked during life as a factor of possible aetiological importance. One was that of a man of 56 in whom a study of the brain was particularly requested because "the patient's experiences as a boxer may have contributed to his dementia". At necropsy the brain weight was 950 grams, the blood vessels were normal, and the only localized lesion was a small scar in the corpus callosum (presumably a tear due to past injury). A moderate degree both of cortical atrophy and of hydrocephalus was



present. The essential histological findings were the same as those seen in Alzheimer's Disease.

In the second case, a man of 63 with a history of past championship boxing and severe memory defect for twenty years, was admitted with a diagnosis of "Organic Dementia, presenile or punch-drunk". Again, after death four years later, the salient features were those of Alzheimer's Disease, although in addition there was also a haemorrhage destroying the pallidum on one side, with considerable hyaline thickening of the smaller vessels throughout the hemispheres.

#### CONCLUSIONS

The possibility of coincidence in each case can never be ruled out and it is certainly not claimed here that any one of the various pathological changes under discussion has ever been proved to have been caused by trauma. On the other hand, enough evidence does seem to have accumulated to justify seriously considering the possibility, and the association might therefore be usefully kept in mind when dealing with similar cases in the future.

The first essential, however, in view of the extraordinary lack of satisfactory pathological information on the subject, is to follow all possible cases through to the end, for even if the underlying pathological changes only rarely turn out to be those described here, it would be equally interesting to know what else might be found.

#### SUMMARY

A case of progressive dementia following a head injury is described in which the neuropathological findings were those of Alzheimer's Disease.

Reports of other rather similar cases, especially in relation to boxing, are summarized. The possible relation of trauma to the onset of dementia and to the pathological changes is briefly discussed.

The remarkable lack of information on this subject is pointed out.

#### ACKNOWLEDGMENTS

We are particularly grateful to Dr. R. Ström-Olsen, Physician Superintendent of Runwell Hospital, for permission to report this case, and to him and to Dr. G. A. Foulds, Dr. G. A. Hendry, Dr. S. L. Last and Dr. H. Williams for their generous co-operation when compiling the history. We would also like to thank Dr. Sabina Strich and Dr. S. Krauss for allowing us to quote the details of the first of the two boxers mentioned by us in the discussion.

We are greatly indebted to Professor Alfred Meyer and Professor Peter Daniel for their invaluable advice and criticism during the preparation of this report.

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# MICROCEPHALY

By

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SMALLNESS of the cranium is one of the commonest findings in severe mental defect. Ashby and Stuart (1933 and 1934) found a correlation between brain weight and mental age of  $+0.15$ , but they regarded this as part of the more general positive correlation of  $+0.24$  which they observed between body weight and mental age. In discussing this subject elsewhere (Hilliard and Kirman, 1957), Crome and Kirman have taken a more definite stand on this matter in so far as idiocy and imbecility are concerned and regard reduced brain weight, which is so often associated with a small cranium, as one of the major factors in reduced intelligence. Crome (1957) found marked reduction in size to be the commonest abnormality in brains of low-grade defectives.

The purpose of this paper is to examine the incidence of microcephaly among low-grade mental defectives in general, and in certain syndromes in particular; to consider the nature of the syndrome and its aetiology; and to formulate some conclusions which may be of value to those who are asked for advice as to the possibility of further children being affected by this condition.

The material presented here is derived from patients in the Fountain Hospital Group which provides for some 800 patients, most of them children of idiot or imbecile level, admitted under the age of 5 years.

## DEFINITION

The term "microcephaly" is used loosely and lacks precision. If the term is to be valuable for purposes of prognosis, investigation of aetiology, or for study of genetics, then it is essential to use measurements and to relate these to norms for age and sex. For our purpose we have considered all cases with a cranial circumference smaller than three standard deviations below the mean for the age and sex. This definition is similar to that proposed by Bööck *et al.* (1953), though they do not take sex into account. These authors also suggested that no data were then available which would allow of the practical application of their definition. We have used as a basis for comparison the norms provided by Westropp and Barber (1956) which are set out in Table I. These norms relate to head circumference, which we have used as a critical measurement throughout. Adequate standardization for the age ranges above 7 years is more difficult, but the Vickers and Stuart (1943) figures go up to the age of 10 years, though they are somewhat less satisfactory in several respects for our purposes than the British data. We are aware that exception can be taken to the use of the head circumference for this purpose since it does not provide full information

TABLE I\*

*Head Circumference for Boys and Girls During the First Seven Years of Life*

| Age         | Boys   |            |       | Girls  |            |       |
|-------------|--------|------------|-------|--------|------------|-------|
|             | Number | Mean (cm.) | S.D.  | Number | Mean (cm.) | S.D.  |
| 1 month ..  | 295    | 37·3       | ±1·54 | 282    | 36·5       | ±1·41 |
| 3 months .. | 229    | 40·7       | ±1·43 | 230    | 39·8       | ±1·39 |
| 6 months .. | 275    | 43·6       | ±1·45 | 262    | 42·5       | ±1·42 |
| 9 months .. | 247    | 45·7       | ±1·40 | 259    | 44·6       | ±1·41 |
| 1 year ..   | 289    | 46·8       | ±1·40 | 275    | 45·6       | ±1·22 |
| 1½ years .. | 255    | 47·9       | ±1·40 | 255    | 47·0       | ±1·30 |
| 2 years ..  | 264    | 49·1       | ±1·47 | 260    | 48·0       | ±1·32 |
| 2½ years .. | 219    | 49·8       | ±1·39 | 221    | 48·8       | ±1·35 |
| 3 years ..  | 216    | 50·4       | ±1·35 | 227    | 49·5       | ±1·35 |
| 3½ years .. | 226    | 51·0       | ±1·40 | 222    | 50·1       | ±1·45 |
| 4 years ..  | 233    | 51·2       | ±1·41 | 229    | 50·7       | ±1·46 |
| 4½ years .. | 220    | 51·6       | ±1·45 | 217    | 51·0       | ±1·48 |
| 5 years ..  | 224    | 51·8       | ±1·47 | 225    | 51·2       | ±1·50 |
| 7 years ..  | 187    | 52·7       | ±1·48 | 194    | 52·2       | ±1·37 |

\* Reproduced from Westropp and Barber (1956).

about the cranial capacity. We considered, however, that this shortcoming would be minimized by the size of the clinical material available. Another argument in favour of the use of the head circumference is that fact that this measurement is now commonly recorded in children's departments of hospitals and clinics so that records are often available for children, dating back to early infancy. Comparable data can also often be obtained on deceased patients and on siblings and other relatives who are not available for measurement.

Böök and his colleagues propose, in their definition of microcephaly, to exclude cases due to premature synostosis of the cranium. Whilst our view is that this is an extremely rare cause of microcephaly, there is some difference of opinion on the subject and it would seem undesirable, in the present state of our knowledge, to make any such arbitrary distinction.

In dealing with microcephaly, we are not primarily concerned with small-headedness which forms a part of one of the clinical entities within the field of mental defect, such as mongolism or phenylketonuria, since we assumed that reduction of head size in these conditions is attributable to the same factors which cause other features of the disease, though those cases with small heads may be regarded as severe forms of the condition. None the less, we propose in this paper to give some consideration to small-headedness within specific syndromes, in order to obtain a broad view of the subject.

The limitations of the earlier criteria of microcephaly are obvious, in that little account was taken of age. Thus, Brushfield and Wyatt (1926) working at this Hospital, found that, of 1,185 children under the age of 8 years, 147 had a head circumference of less than  $17\frac{1}{2}$  inches. Reference to the Westropp and Barber norms shows, however, that the significance of such a measurement would vary greatly at different ages.

The question of the possible sub-division of microcephaly into various groups, including the problem of "true" microcephaly, will be reviewed later in this paper in the light of the evidence available from our data.

#### INCIDENCE OF MICROCEPHALY

Table II shows the incidence of microcephaly among 100 consecutive admissions to the Fountain Hospital. Most of these children are of idiot or



imbecile level, though an occasional admission proves to have a somewhat higher level of intelligence. Apart from cases of mongolism, no attempt has been made to distinguish different clinical varieties of microcephaly at this stage.

TABLE II  
*Incidence of Microcephaly in 100 Consecutive Admissions*

| No. of Patient | Sex | Age   | Head Circumference on Admission | Average Head Circumference for Age and Sex | Average Head Circumference Less 3 S.D. | Indexed Diagnosis                                                                                                                     |
|----------------|-----|-------|---------------------------------|--------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
|                |     |       | (cm.)                           | (cm.)                                      | (cm.)                                  |                                                                                                                                       |
| 1. .. F        | 6   | 10/12 | 48.9                            | 52.2                                       | 48.29                                  | Cerebral palsy. Spastic diplegia.                                                                                                     |
| 2. .. M        | 1   | 7/12  | 42.5                            | 47.9                                       | 43.70                                  | Phenylketonuria.                                                                                                                      |
| 3. .. F        | 3   |       | 50.1                            | 49.5                                       | 45.45                                  | Phenylketonuria.                                                                                                                      |
| 4. .. M        | 4   | 6/12  | 48.3                            | 51.6                                       | 47.25                                  | Premature.                                                                                                                            |
| 5. .. M        | 2   | 11/12 | 47.6                            | 50.4                                       | 46.35                                  | Premature.                                                                                                                            |
| 6. .. M        | 3   | 1/12  | 47.0                            | 50.4                                       | 46.45                                  | Phenylketonuria. Chorea. Cerebral palsy                                                                                               |
| 7. .. M        | 3   | 7/12  | 48.3                            | 51.0                                       | 46.80                                  | Phenylketonuria.                                                                                                                      |
| 8. .. M        | 2   | 1/12  | 44.5                            | 49.1                                       | 44.69                                  | Microcephaly. Cerebral palsy. Strabismus. Spastic diplegia. Skull, asymmetry of. Illegitimate.                                        |
| 9. .. F        | 3   | 5/12  | 45.7                            | 50.1                                       | 45.75                                  | Phenylketonuria.                                                                                                                      |
| 10. .. M       | 1   | 5/12  | 46.4                            | 47.9                                       | 43.70                                  | Phenylketonuria.                                                                                                                      |
| 11. .. M       | 1   |       | 43.8                            | 46.8                                       | 42.60                                  | Phenylketonuria.                                                                                                                      |
| 12. .. M       | 3   | 5/12  | 48.3                            | 51.0                                       | 46.80                                  | Petit mal. ? Familial. Caesarean birth.                                                                                               |
| 13. .. M       | 1   | 3/12  | 43.2                            | 46.8                                       | 42.60                                  | Epilepsy. Spastic diplegia. Strabismus. Birth injury. Blind. Cerebral palsy. Skull, asymmetry of.                                     |
| 14. .. M       | 2   | 3/12  | 45.7                            | 49.1                                       | 44.69                                  | —                                                                                                                                     |
| 15. .. F       | 2   | 9/12  | 59.0                            | 48.8                                       | 44.75                                  | Hydrocephalus. Cerebral palsy. Nystagmus. Strabismus. Spastic diplegia.                                                               |
| 16. .. F       | 3   | 2/12  | 40.6                            | 49.5                                       | 45.45                                  | Microcephaly. Strabismus.                                                                                                             |
| 17. .. M       | 3   | 4/12  | 45.1                            | 51.0                                       | 46.80                                  | Cerebral palsy. Epilepsy—petit mal. Breech. Birth injury.                                                                             |
| 18. .. M       |     | 11/12 | 46.4                            | 46.8                                       | 42.60                                  | Dislocation of hip. Blind. Familial. Cerebral palsy. Epilepsy. Strabismus. Nystagmus.                                                 |
| 19. .. M       | 2   | 5/12  | 48.3                            | 46.8                                       | 45.63                                  | Blind. Toxaemia of pregnancy.                                                                                                         |
| 20. .. F       | 3   | 6/12  | 49.5                            | 50.1                                       | 45.75                                  | Phenylketonuria.                                                                                                                      |
| 21. .. M       | 2   | 5/12  | 49.5                            | 49.8                                       | 45.63                                  | Mongolism. Icterus gravis neonatorum.                                                                                                 |
| 22. .. M       | 2   |       | 43.8                            | 49.1                                       | 44.69                                  | Twin. Birth injury. Cerebral palsy. Spastic diplegia. Premature.                                                                      |
| 23. .. F       | 6   | 6/12  | 48.9                            | 52.2                                       | 48.29                                  | Premature. Twin. Familial.                                                                                                            |
| 24. .. F       | 6   | 6/12  | 48.9                            | 52.2                                       | 48.29                                  | ?Gastro-enteritis, effects of. Premature Twin. Familial.                                                                              |
| 25. .. F       | 3   | 7/12  | 47.6                            | 50.1                                       | 45.75                                  | Cerebral palsy. Chorea. Epilepsy—petit mal.                                                                                           |
| 26. .. M       | 3   |       | 50.8                            | 50.4                                       | 46.35                                  | Familial? Meningitis (meningococcal). Premature.                                                                                      |
| 27. .. M       | 1   | 4/12  | 47.0                            | 47.9                                       | 43.70                                  | —                                                                                                                                     |
| 28. .. M       | 1   | 1/12  | 43.2                            | 46.8                                       | 42.60                                  | Icterus gravis neonatorum. Premature. Skull, asymmetry of.                                                                            |
| 29. .. M       | 5   | 3/12  | 49.5                            | 51.8                                       | 47.39                                  | —                                                                                                                                     |
| 30. .. M       | 6   | 7/12  | 55.2                            | 52.7                                       | 48.26                                  | ?Birth injury. Cerebral palsy. Toxaemia of pregnancy. Ataxia. Cleft palate. Meningitis—tuberculous.                                   |
| 31. .. M       | 5   |       | 48.9                            | 51.8                                       | 47.39                                  | Mongolism.                                                                                                                            |
| 32. .. M       | 4   | 1/12  | 42.5                            | 51.2                                       | 46.97                                  | Familial. Psychosis—maternal. Microcephaly. Cerebral palsy. Spastic diplegia.                                                         |
| 33. .. M       | 6   | 5/12  | 47.0                            | 52.3                                       | 48.26                                  | Strabismus. Epilepsy. Gastro-enteritis, effects of.                                                                                   |
| 34. .. M       | 3   | 11/12 | 48.9                            | 51.2                                       | 46.97                                  | Nystagmus. Strabismus.                                                                                                                |
| 35. .. F       | 4   | 9/12  | 48.3                            | 51.2                                       | 46.56                                  | ?Deaf. Premature. Athetosis. Cerebral palsy. Strabismus.                                                                              |
| 36. .. F       | 5   | 8/12  | 50.8                            | 51.7                                       | 46.70                                  | —                                                                                                                                     |
| 37. .. M       | 4   | 8/12  | 47.6                            | 51.6                                       | 47.25                                  | Strabismus. Mongolism.                                                                                                                |
| 38. .. M       | 3   | 2/12  | 49.5                            | 50.4                                       | 46.35                                  | —                                                                                                                                     |
| 39. .. F       | 4   | 7/12  | 42.5                            | 51.2                                       | 46.56                                  | ?Lens opacities. ?Retrolental fibroplasia. Cerebral palsy. Hemiplegia, left. Strabismus, internal. Premature. Meningitis, influenzal. |
| 40. .. F       | 1   | 4/12  | 43.2                            | 47.9                                       | 43.10                                  | Mongolism.                                                                                                                            |
| 41. .. M       | 2   | 5/12  | 45.7                            | 49.8                                       | 45.63                                  | ?Macular degeneration (exudate). Premature. Obscure retinopathy. Optic atrophy.                                                       |
| 42. .. M       | 3   | 5/12  | 47.1                            | 51.0                                       | 46.80                                  | Cerebral palsy. Hemiplegia, left. Epilepsy. Strabismus, external. Birth injury.                                                       |
| 43. .. M       | 6   | 5/12  | 48.3                            | 52.3                                       | 48.26                                  | Toxaemia of pregnancy. Familial.                                                                                                      |
| 44. .. F       | 4   | 10/12 | 47.1                            | 51.2                                       | 46.70                                  | Epileptic. Cerebral palsy—atonic variety.                                                                                             |
| 45. .. M       | 2   | 4/12  | 48.3                            | 49.8                                       | 45.63                                  | Twin.                                                                                                                                 |
| 46. .. F       | 1   | 7/12  | 53.3                            | 47.0                                       | 43.10                                  | Hydrocephalus.                                                                                                                        |
| 47. .. M       | 3   | 8/12  | 47.1                            | 51.0                                       | 46.80                                  | Mongolism.                                                                                                                            |
| 48. .. M       | 3   | 9/12  | 53.3                            | 51.0                                       | 46.80                                  | Epilepsy.                                                                                                                             |
| 49. .. F       | 9   | 7/12  | 50.8                            | 52.2                                       | 48.29                                  | Abortion—attempted. Psychotic features.                                                                                               |
| 50. .. F       | 3   | 8/12  | 48.3                            | 50.1                                       | 45.75                                  | Pregnancy—bleeding in. Cerebral palsy. Athetosis. Strabismus.                                                                         |

TABLE II—(continued)

| No. of Patient | Sex | Age     | Head Circumference on Admission (cm.) | Average Head Circumference for Age and Sex (cm.) | Average Head Circumference Less 3 S.D. (cm.) | Indexed Diagnosis                                                                                          |
|----------------|-----|---------|---------------------------------------|--------------------------------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------------|
| 51. ..         | M   | 5 4/12  | 48·3                                  | 51·8                                             | 47·39                                        | Mongolism.                                                                                                 |
| 52. ..         | M   | 4 10/12 | 48·3                                  | 51·8                                             | 47·39                                        | Illegitimate. Cataract. Galactosuria. Icterus gravis neonatorum. Skull, asymmetry of.                      |
| 53. ..         | F   | 2 10/12 | 45·7                                  | 49·5                                             | 45·45                                        | Mongolism.                                                                                                 |
| 54. ..         | M   | 2 9/12  | 40·6                                  | 50·4                                             | 45·63                                        | Strabismus. Microcephaly. Cerebral palsy. Spastic diplegia. Epilepsy. Optic atrophy.                       |
| 55. ..         | F   | 3 4/12  | 45·7                                  | 51·0                                             | 45·75                                        | Nystagmus. Strabismus. Cerebral palsy. Spastic diplegia.                                                   |
| 56. ..         | M   | 2 6/12  | 47·1                                  | 49·8                                             | 45·63                                        | Mongolism. Strabismus. Nystagmus                                                                           |
| 57. ..         | M   | 5 8/12  | 52·1                                  | 52·3                                             | 47·39                                        | Epilepsy. Cerebral palsy. Deaf. Meningitis—tuberculous. Hemiplegia, right. Skull deformity. Optic atrophy. |
| 58. ..         | M   | 2 11/12 | 47·1                                  | 50·4                                             | 46·35                                        | Mongolism.                                                                                                 |
| 59. ..         | F   | 3       | 46·4                                  | 49·5                                             | 45·45                                        | Icterus gravis neonatorum. Strabismus. Cerebral palsy. Spastic diplegia.                                   |
| 60. ..         | F   | 3 10/12 | 48·3                                  | 50·7                                             | 46·32                                        | Mongolism.                                                                                                 |
| 61. ..         | F   | 2 3/12  | 45·7                                  | 49·1                                             | 44·04                                        | Pregnancy—bleeding in. Premature. Strabismus.                                                              |
| 62. ..         | M   | 3 10/12 | 45·1                                  | 51·2                                             | 46·97                                        | Mongolism.                                                                                                 |
| 63. ..         | M   | 6 8/12  | 53·3                                  | 52·7                                             | 48·26                                        | Familial. Epileptic.                                                                                       |
| 64. ..         | M   | 4 2/12  | 50·8                                  | 51·2                                             | 46·97                                        | Mongolism.                                                                                                 |
| 65. ..         | M   | 3 4/12  | 47·1                                  | 51·0                                             | 46·80                                        | Toxaemia of pregnancy. Cerebral palsy. Spastic diplegia.                                                   |
| 66. ..         | M   | 10 5/12 | 50·8                                  | 52·7                                             | 48·26                                        | Keratitis, interstitial. Corneal opacity.                                                                  |
| 67. ..         | M   | 3 8/12  | 47·1                                  | 51·0                                             | 46·80                                        | Mongolism.                                                                                                 |
| 68. ..         | F   | 4 5/12  | 50·8                                  | 51·0                                             | 46·56                                        | Deafness? Epileptic. ?Encephalitis.                                                                        |
| 69. ..         | F   | 2 8/12  | 48·3                                  | 48·8                                             | 44·75                                        | Cerebral palsy. Spastic diplegia. Meningitis—tuberculous. Strabismus.                                      |
| 70. ..         | F   | 4       | 49·5                                  | 50·7                                             | 46·32                                        | Caesarean section. Hemiplegia, left. Strabismus. Nystagmus                                                 |
| 71. ..         | M   | 2 10/12 | 45·7                                  | 50·4                                             | 46·35                                        | Epilepsy. Skull, asymmetry of.                                                                             |
| 72. ..         | M   | 2 10/12 | 48·3                                  | 50·4                                             | 46·35                                        | ?Deaf. Icterus neonatorum. Rhesus factor incompatibility.                                                  |
| 73. ..         | M   | 2 8/12  | 49·5                                  | 49·8                                             | 45·63                                        | ?Deaf.                                                                                                     |
| 74. ..         | F   | 10 1/12 | 50·8                                  | 52·2                                             | 48·29                                        | Ataxia. Cerebral palsy.                                                                                    |
| 75. ..         | F   | 5 3/12  | 48·3                                  | 51·2                                             | 46·70                                        | Premature. Psychosis—maternal. Birth injury.                                                               |
| 76. ..         | F   | 5 6/12  | 42·9                                  | 51·7                                             | 46·70                                        | Ataxia. Cataract Cerebral palsy. Strabismus. Microcephaly. Prematurity. Spina-bifida occulta.              |
| 77. ..         | M   | 2 2/12  | 74·9                                  | 49·1                                             | 44·69                                        | Hydrocephalus. Blind. Consanguinity.                                                                       |
| 78. ..         | M   | 4 4/12  | 48·3                                  | 51·2                                             | 47·25                                        | —                                                                                                          |
| 79. ..         | F   | 5       | 40·0                                  | 51·2                                             | 46·70                                        | Prematurity. Microcephaly. Strabismus. Irradiation, effects of.                                            |
| 80. ..         | F   | 9       | 49·5                                  | 52·2                                             | 48·29                                        | Mongolism.                                                                                                 |
| 81. ..         | M   | 5       | 47·1                                  | 51·8                                             | 47·39                                        | Mongolism. Strabismus.                                                                                     |
| 82. ..         | M   | 1 10/12 | 43·8                                  | 49·1                                             | 44·69                                        | Ataxia. Strabismus. Epilepsy. Birth injury. Cerebral palsy.                                                |
| 83. ..         | M   | 1 3/12  | 41·9                                  | 46·8                                             | 42·60                                        | Mongolism.                                                                                                 |
| 84. ..         | F   | 6 7/12  | 48·3                                  | 52·2                                             | 48·29                                        | —                                                                                                          |
| 85. ..         | M   | 1 7/12  | 64·8                                  | 47·9                                             | 43·70                                        | Hydrocephalus. Spina bifida. Strabismus Cerebral palsy.                                                    |
| 86. ..         | M   | 2       | 45·1                                  | 49·1                                             | 44·69                                        | Cerebral palsy. Athetosis. Epilepsy. Skull, asymmetry of.                                                  |
| 87. ..         | M   | 3 11/12 | 46·4                                  | 51·2                                             | 46·97                                        | —                                                                                                          |
| 88. ..         | F   | 5 4/12  | 50·1                                  | 51·8                                             | 46·70                                        | Phenylketonuria. Familial. Spina bifida occulta. Toxaemia of pregnancy.                                    |
| 89. ..         | F   | 3 10/12 | 46·3                                  | 50·7                                             | 46·32                                        | Cleft palate.                                                                                              |
| 90. ..         | M   | 5       | 44·5                                  | 51·8                                             | 47·39                                        | Familial. Ichthyosis. Pyloric stenosis.                                                                    |
| 91. ..         | M   | 2 10/12 | 47·6                                  | 50·4                                             | 46·35                                        | Asphyxia neonatorum. Hypertelorism. Strabismus. external. Epilepsy.                                        |
| 92. ..         | F   | 4 5/12  | 45·1                                  | 51·0                                             | 46·56                                        | Mongolism. Cataract, bilateral.                                                                            |
| 93. ..         | M   | 4 11/12 | 51·4                                  | 51·8                                             | 47·39                                        | Epilepsy. Illegitimate. Familial. Psychotic features.                                                      |
| 94. ..         | F   | 3 1/12  | 45·1                                  | 49·5                                             | 45·45                                        | Familial. Spina bifida occulta.                                                                            |
| 95. ..         | M   | 2 2/12  | 50·2                                  | 49·1                                             | 44·69                                        | Strabismus, Right ptosis. Epileptic.                                                                       |
| 96. ..         | M   | 3 8/12  | 48·3                                  | 51·0                                             | 46·80                                        | —                                                                                                          |
| 97. ..         | M   | 4 3/12  | 37·5                                  | 51·2                                             | 46·97                                        | Premature. Strabismus. Microcephaly. Microphthalmia. Spina bifida, occulta.                                |
| 98. ..         | F   | 4       | 48·9                                  | 50·7                                             | 46·32                                        | Epileptic. Pinna, malformation of. Twin. Toxaemia of pregnancy.                                            |
| 99. ..         | F   | 1 7/12  | 41·9                                  | 47·0                                             | 43·10                                        | Mongolism.                                                                                                 |
| 100. ..        | M   | 1 11/12 | 44·5                                  | 49·1                                             | 44·69                                        | ?Mongolism.                                                                                                |

Microcephalic measurements are italicized in Column 4 (excluding those due to mongolism).

Twenty-six of the 100 patients had a head circumference which was more than three standard deviations below the mean. Of these, six were children with mongolism, leaving 20 who might be classed as microcephalic. This incidence is higher than that found by Brushfield and Wyatt, presumably because of the different criteria used. Microcephaly as defined for our purpose

is usually associated with imbecility or idiocy and only rarely with feeble-mindedness (this question is referred to subsequently). Since rather more than half of the patients in mental deficiency hospitals are classed as feeble-minded (O'Connor and Tizard, 1956), it follows that the proportion of microcephaly in most mental deficiency hospitals should be of the order of 10 per cent. or somewhat less. The fact that microcephalics tend to die early would tend to reduce this estimate still further. Penrose's (1938) figure is 1.7 per cent. of cases of "the traditional type" of microcephaly in an institutional population, i.e. 22 out of 1,280 patients. He does not say, however, how many patients not of the traditional type had little heads.

In defining microcephaly in this connection, Penrose states that the head is significantly smaller than that of other patients of the same mental grade. It will be seen from Figure 1 that there is indeed a marked mean reduction of

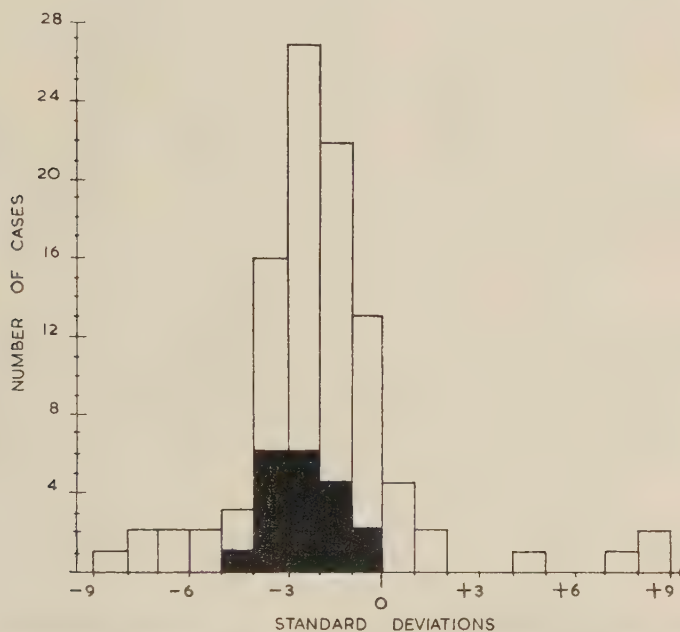


FIG. 1.—One hundred consecutive admissions to Fountain Hospital showing distribution of head circumference in relation to mean. Cases of mongolism are shown in black.

cranial circumference for the group of cases of severe mental defect as a whole: the mean of the group falling between 2 and 3 standard deviations below the mean of normal children. None the less, it is convenient to take for special consideration the group which falls below the limits we have specified, since reduction in head size is in them a leading feature of their abnormality.

It is probable that in this, say 20 per cent., of imbeciles and idiots with small heads, we are dealing with cases due to specific factors producing small-headedness, e.g. specific genetic factors or irradiation; we are also studying the action of certain factors which in milder form produce some interference with brain development and function, but which in exceptional instances produce microcephaly. Such factors are, for example, those producing occasional cases



with phenylketonuria or rubella embryopathy. A further example is provided by a recently admitted 14 month girl with sucrosuria and a head circumference of  $15\frac{3}{4}$  inches (40 cm.).

### SKULL CIRCUMFERENCE POST-MORTEM

Table III gives the skull measurements and brain weight of a series of 64 children under the age of 5 years and 3 months, dying at the Fountain Hospital.

TABLE III  
*Head Circumference, Cranial Index and Brain Weight in 64 Mental Defectives  
Examined Post-mortem*

|                |               |              | Head Circumference     |      | Cranial Index | Brain Weight (Gm.) | Notes |
|----------------|---------------|--------------|------------------------|------|---------------|--------------------|-------|
| No. of Patient | Age at Death  | Actual (cm.) | Mean Less 3 S.D. (cm.) |      |               |                    |       |
| 1              | .. .. 1 3/12  | 46.4         | 42.60                  | 0.72 | 1,003         |                    |       |
| 2              | .. .. 1 2/12  | 40           | 41.94                  | 0.91 | 730           | Mongolism          |       |
| 3              | .. .. 1 3/12  | 44.5         | 43.70                  | 0.94 | 970           | Mongolism          |       |
| 4              | .. .. 9/12    | 42           | 41.50                  | 0.92 | 810           | Mongolism          |       |
| 5              | .. .. 10/12   | 44.5         | 40.37                  | 0.86 | 780           |                    |       |
| 6              | .. .. 5/12    | 38           | 39.25                  | 0.64 | 610           | Acrocephaly        |       |
| 7              | .. .. 1 1/12  | 60           | 41.94                  | 0.86 | —             |                    |       |
| 8              | .. .. 1 7/12  | 44           | 43.10                  | 0.66 | 705           |                    |       |
| 9              | .. .. 1 9/12  | 40           | 44.69                  | 0.86 | 540           |                    |       |
| 10             | .. .. 1 4/12  | 34           | 43.10                  | 0.82 | 220           |                    |       |
| 11             | .. .. 1 4/12  | 40.5         | 43.70                  | 0.78 | 630           |                    |       |
| 12             | .. .. 11/12   | 43.5         | 42.60                  | 0.80 | 725           |                    |       |
| 13             | .. .. 1 8/12  | 41.5         | 43.10                  | 0.89 | 755           | Mongolism          |       |
| 14             | .. .. 1 7/12  | 42           | 43.70                  | 0.92 | 530           |                    |       |
| 15             | .. .. 1 9/12  | 41.8         | 43.70                  | 0.89 | 760           | Mongolism          |       |
| 16             | .. .. 1 6/12  | 61           | 43.70                  | 0.94 | ?             |                    |       |
| 17             | .. .. 1 6/12  | 44           | 43.70                  | 0.72 | 880           |                    |       |
| 18             | .. .. 1 7/12  | 43           | 43.10                  | 0.91 | 820           | Mongolism          |       |
| 19             | .. .. 2       | 43.5         | 44.69                  | 0.79 | 810           |                    |       |
| 20             | .. .. 2 1/12  | 43           | 44.04                  | 0.76 | 560           |                    |       |
| 21             | .. .. 1 11/12 | 42.5         | 44.69                  | 0.88 | 765           |                    |       |
| 22             | .. .. 1 11/12 | 54.5         | 44.04                  | 0.76 | ?             |                    |       |
| 23             | .. .. 2       | 43.5         | 44.69                  | 0.77 | 430           |                    |       |
| 24             | .. .. 1 10/12 | 48           | 44.69                  | 0.81 | 1,130         |                    |       |
| 25             | .. .. 2 3/12  | 46           | 45.63                  | 0.88 | 1,125         |                    |       |
| 26             | .. .. 1 10/12 | 58           | 44.69                  | 0.76 | ?             |                    |       |
| 27             | .. .. 2 3/12  | 44.5         | 44.04                  | 0.73 | 795           |                    |       |
| 28             | .. .. 2       | 47           | 44.69                  | 0.83 | 1,100         |                    |       |
| 29             | .. .. 2 1/12  | 41.6         | 44.69                  | 0.85 | 660           |                    |       |
| 30             | .. .. 2 8/12  | 47           | 45.63                  | 0.79 | 975           |                    |       |
| 31             | .. .. 2 4/12  | 40           | 45.63                  | 0.75 | 490           |                    |       |
| 32             | .. .. 3 1/12  | 44.5         | 46.35                  | 0.85 | 915           | Mongolism          |       |
| 33             | .. .. 3 1/12  | 43.5         | 45.45                  | 0.94 | 910           | Mongolism          |       |
| 34             | .. .. 3 2/12  | 45.5         | 45.45                  | 0.79 | 1,027         |                    |       |
| 35             | .. .. 2 11/12 | 44.3         | 46.35                  | 0.85 | 890           | Mongolism          |       |
| 36             | .. .. 3       | 45.5         | 45.45                  | 0.94 | 860           |                    |       |
| 37             | .. .. 3       | 45.6         | 45.45                  | 0.83 | 1,010         |                    |       |
| 38             | .. .. 2 11/12 | 45           | 46.35                  | 0.82 | 1,005         | Mongolism          |       |
| 39             | .. .. 3 2/12  | 47.1         | 45.45                  | —    | 1,015         |                    |       |
| 40             | .. .. 3 1/12  | 43.7         | 45.45                  | 0.93 | 870           | Mongolism          |       |
| 41             | .. .. 3 5/12  | 42.6         | 46.80                  | 1.03 | 745           | Mongolism          |       |

TABLE III (continued)

| No. of Patient | Age at Death | Head Circumference |                        | Cranial Index | Brain Weight (Gm.) | Notes       |
|----------------|--------------|--------------------|------------------------|---------------|--------------------|-------------|
|                |              | Actual (cm.)       | Mean Less 3 S.D. (cm.) |               |                    |             |
| 42             | .. 3 7/12    | 47                 | 46.80                  | 0.82          | 1,075              |             |
| 43             | .. 3 6/12    | 39.5               | 46.80                  | 0.86          | 785                |             |
| 44             | .. 3 9/12    | 47                 | 46.97                  | 0.72          | 1,340              |             |
| 45             | .. 3 6/12    | 42.5               | 46.80                  | —             | 840                | Mongolism   |
| 46             | .. 3 8/12    | 54                 | 45.75                  | 0.68          | 1,080              |             |
| 47             | .. 3 10/12   | 46                 | 46.97                  | 0.85          | 895                |             |
| 48             | .. 3 11/12   | 46                 | 46.32                  | 0.82          | 1,000              |             |
| 49             | .. 4 2/12    | 54                 | 46.97                  | 0.80          | 1,665              |             |
| 50             | .. 4         | 45                 | 46.97                  | 0.87          | 745                |             |
| 51             | .. 4 2/12    | 38.5               | 46.97                  | 0.85          | 515                |             |
| 52             | .. 4         | 44                 | 46.97                  | 0.72          | 875                |             |
| 53             | .. 3 10/12   | 46                 | 46.97                  | 1.21          | 1,020              | Mongolism   |
| 54             | .. 4         | 51                 | 46.97                  | —             | 1,295              |             |
| 55             | .. 4 4/12    | 49.6               | 47.25                  | 1.04          | 1,330              | Mongolism   |
| 56             | .. 4 6/12    | 44                 | 46.56                  | 0.83          | 795                |             |
| 57             | .. 4 6/12    | 51.5               | 47.25                  | 0.69          | 1,440              |             |
| 58             | .. 4 11/12   | 42.3               | 46.70                  | 0.84          | 640                |             |
| 59             | .. 5 3/12    | 48                 | 46.70                  | 0.86          | 1,060              |             |
| 60             | .. 4 10/12   | 42.5               | 47.39                  | 0.88          | 765                |             |
| 61             | .. 4 10/12   | 46.5               | 46.70                  | 0.97          | 960                | Mongolism   |
| 62             | .. 4 11/12   | 45                 | 46.70                  | 1.02          | 1,345              | Acrocephaly |
| 63             | .. 5 1/12    | 48                 | 47.39                  | 0.79          | 1,100              |             |
| 64             | .. 5 1/12    | 49.5               | 47.39                  | 0.81          | 875                |             |

All cases below this age, on whom an adequate post-mortem examination had been completed, were included. This number was derived from 91 consecutive deaths in this age group. In 12 cases, permission for post-mortem examination was refused; in 7, adequate particulars are not available; and in 8, the post-mortem was carried out by the coroner's pathologist and a detailed report was not furnished.

It was thought that the measurements obtained in this way might be slightly more reliable than those carried out in the course of the clinical examinations when the children are often restless and difficult to measure. It was considered, however, that the post-mortem sample would contain a high proportion of microcephalics, particularly those of severe degree and those complicated by cerebral palsy, since the expectation of life in these groups is poor.

In fact, 34, or just over half, of the children dying in this series of 64 had head circumferences which placed them in the microcephalic range. Thirteen of these 34 children were cases of mongolism, one of classical acrocephaly-syndactyly and one acrocephaly. If these are excluded, there remain 19 microcephalics, constituting 30 per cent. of the total, as opposed to 20 per cent. of the series of admissions. This strengthens the impression that mentally defective children with small heads are more liable to die early than those who have larger heads. This finding also applies to the cases of mongolism since, out of 16 children with this condition in the post-mortem group, 13 could be classed as microcephalic, a proportion of 81 per cent. compared with 33 per cent. of young children with mongolism at present in a ward in the hospital.

Since measurements of length and breadth of the skull were available in most of the post-mortem cases, it was thought that an examination of cranial index might be useful. Data on 19 cases of microcephaly and 30 other mental

defectives were compared. For this purpose also, the children with mongolism were excluded. It was found that the average cranial index for the microcephalic children at post-mortem was 0.83, whilst that for the non-microcephalic children was 0.76. It appears clear from these facts that, even if mongolism is excluded, there is no tendency for children with small heads to be relatively long headed. This is of interest in view of the general belief summarized by Penrose (1954) that there is "A class of cases clinically distinguished from the rest of defectives by the fact that the head is diminished greatly in the vertical measurement and in width, but is less abnormal in length . . . These cases with low cephalic index can be fairly well distinguished from the rest . . ." Penrose goes on to say that "The group of relatively long-headed microcephalics includes a type which is due to a single recessive gene and which has been termed 'true microcephaly'." There was insufficient material in the post-mortem cases to provide a significant comparison between a presumed genetic group and other cases of microcephaly. None of these patients was known to be the child of a consanguineous marriage, none was known to have mentally defective siblings and only 2 had other defectives in the family. The cranial indices of these two were 0.88 and 0.79.

#### THE NATURE OF THE SYNDROME

Whilst a number of authorities are agreed on the existence of "true microcephaly", they are not unanimous in their definition of this concept. Penrose, in the passage already quoted, refers to "relatively normal musculature" and a "relatively normal chin". Tredgold (1952), together with a number of other authorities, describes the chin in this condition as "receding", whilst it is interesting to note that Sheldon (1955) chooses a photograph of a child with spastic diplegia to illustrate the condition. In this connection, it should be pointed out that there is a tendency to look upon congenital spastic diplegia as something of a genetic and clinical entity, usually with a normal sized head (Penrose, 1955 and Böök, 1953). Penrose, however, stresses the importance of phenocopies and considers that perhaps a quarter of cases of congenital spastic diplegia are due to recessive genes, whilst Böök admits that a "symptomatological clear-cut diagnosis cannot yet be secured", referring to the syndrome of oligophrenia and congenital spastic diplegia.

Much of the material which has formed the basis in the past of these clinical descriptions is highly selected and it is possible to obtain, as Brushfield and Wyatt (1926) did in studying "true microcephaly", a series of typical cases by the simple process of excluding all those which are atypical. These authors considered that only 70 of their 147 cases conformed to their criteria of "true microcephaly", i.e. 6 per cent. compared with 12 per cent. of all the children in the hospital with small heads. Incidentally, they include among their criteria occipital flattening, which suggests that they were not interested in dolicocephaly as a distinctive feature. Interestingly enough, they found five cases in which an additional sibling was affected but only chose to include two of these among their true microcephalics.

The material presented by Komai and his colleagues (1955) emphasizes the importance of selection in regard to the clinical description, since no less than 44.8 per cent. of their 143 cases were the children of first cousin marriages and the number of sibships involved was only 78. It would appear that their attention must have been directed primarily to the children of consanguineous marriages and to sibships containing more than one example of the condition,



though they do not state this. The incidence of consanguinity among the general population of Japan is assumed by these same authors to be 7 per cent. This would fit in with expectation if all their cases were genetically determined and if the genetically determined form had an incidence of 1/40,000 of the population, i.e. about the same as that of phenylketonuria.

ANALYSIS OF CASE MATERIAL IN THE FOUNTAIN HOSPITAL

In the course of the past 10 years, 118 cases in the Fountain Hospital have been indexed as microcephaly. This number does not include any examples of mongolism or of acrocephaly. For a number of reasons, a few cases fail to be classified in the index. The data on these 118 cases were all scrutinized on the basis of the head circumference at the time of admission, and those instances were excluded where information was lacking or where the circumference was less than three standard deviations below the norm for the age and sex. This left a total of 102 cases which could be studied. Some data on this group of cases are set out in Table IV. In this material there were two consanguineous unions, one of first cousins and one of brother and sister, resulting in affected

TABLE IV

| <i>One Hundred and Eighteen Cases Classed as Microcephaly</i>                             |    |    |    |    |    |    |    |    |     |
|-------------------------------------------------------------------------------------------|----|----|----|----|----|----|----|----|-----|
| <i>Showing Incidence of Microcephaly and Mental Defect in Siblings and Near Relatives</i> |    |    |    |    |    |    |    |    |     |
| Gross total                                                                               | .. | .. | .. | .. | .. | .. | .. | .. | 118 |
| Confirmed by measurement                                                                  | .. | .. | .. | .. | .. | .. | .. | .. | 102 |
| With parental consanguinity                                                               | .. | .. | .. | .. | .. | .. | .. | .. | 2   |
| With microcephalic siblings:                                                              | .. | .. | .. | .. | .. | .. | .. | .. | 6   |
| By measurement                                                                            | .. | .. | .. | .. | .. | .. | .. | .. | 4   |
| No measurement                                                                            | .. | .. | .. | .. | .. | .. | .. | .. | 2   |
| With deformed stillborn sibling                                                           | .. | .. | .. | .. | .. | .. | .. | .. | 2   |
| With non-microcephalic defective sibling                                                  | .. | .. | .. | .. | .. | .. | .. | .. | 1   |
| With other mentally defective relatives*:                                                 | .. | .. | .. | .. | .. | .. | .. | .. | 9   |
| Of which microcephalic                                                                    | .. | .. | .. | .. | .. | .. | .. | .. | 1   |
| Normal head size                                                                          | .. | .. | .. | .. | .. | .. | .. | .. | 4   |
| Hydrocephalic                                                                             | .. | .. | .. | .. | .. | .. | .. | .. | 1   |
| No measurement                                                                            | .. | .. | .. | .. | .. | .. | .. | .. | 3   |

\* 3 of these also had microcephalic siblings and are included above.

patients. In a further 9 cases, there were defective siblings. In 4 of these instances, the sibling was microcephalic on measurements. Of the remainder, one was a stillborn "deformed" twin. Another case was that of a stillborn sibling described as microcephalic. One was "microcephalic, dying 8 days after birth". One defective sibling was not microcephalic, though spastic and suffering from petit mal. The ninth case had a sibling who was hemiplegic at birth, with a small head. No skull measurements were obtained, but the brain weighed 210 g. as compared with the mean for the age of 382 g.

In 9 instances, there were other mental defectives known amongst close relatives. Three of these 9 were also included in the group with microcephalic siblings and one had a microcephalic cousin. In 4 cases, affected relatives were known to have normal-size heads. One defective relative was grossly hydrocephalic. In the remaining 3 cases, details of the head size of the relative are not available.

THE SIGNIFICANCE OF THE CRANIAL INDEX

Of the features mentioned by different authors as characteristic of "true" microcephaly, the only one which lends itself to objective measurement is that

of long-headedness. A comparison is summarized in Table V of the group of cases in which we thought a genetic factor might be implicated and another group in which there was no evidence of any such genetic factor.

TABLE V  
*Cranial Index in Microcephaly*

| Group with:                                            | Number | Average C.I. |
|--------------------------------------------------------|--------|--------------|
| 1. Parental consanguinity .. .. .                      | 5      | .78          |
| 2. Microcephalic siblings .. .. .                      | 15     | .80          |
| 3. Siblings M.D., not microcephalic .. .. .            | 5      | .78          |
| 4. Other relatives microcephalic .. .. .               | 3      | .80          |
| 5. Other relatives M.D., not microcephalic .. .. .     | 11     | .79          |
| 6. Probably environmental origin .. .. .               | 6      | .81          |
| 7. No defective relatives known .. .. .                | 85     | .81          |
| (1 case included in both group 1 and 2)                |        |              |
| A. "Familial" cases, groups 1-5, N=39                  |        | .79          |
| B. Environmentally and unknown cases, groups 6-7, N=91 |        | .81          |
|                                                        | A      | B            |
| Average .. .. .                                        | .79    | .81          |
| Median .. .. .                                         | .79    | .82          |
| S.D. .. .. .                                           | .06    | .11          |

There is no significance in the difference between the two means.

These two groups were made up by bringing together patients from four different sources; those already indexed as microcephalic and mentioned above, additional cases from the 100 admissions and from the post-mortem series, and finally from a special scrutiny of cases classified in our hospital index as "familial".

It will be seen from the details of the sub-groups given in Table V and Figure 2 that the average cranial indices lie very close to each other, suggesting

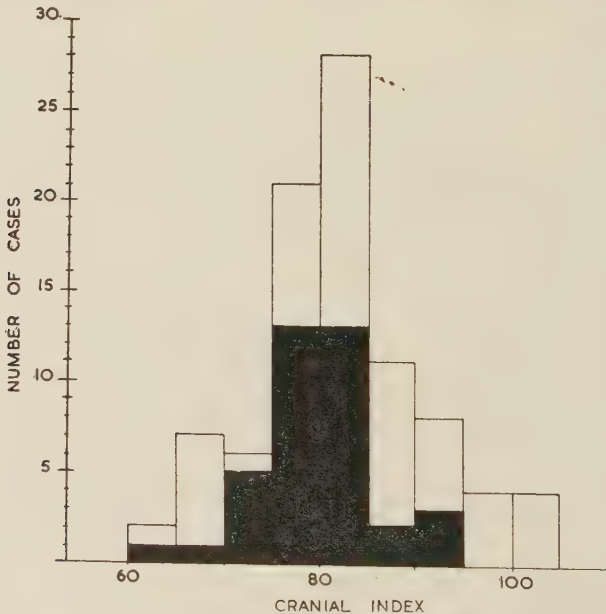


FIG. 2.—Cranial index in microcephaly. The figure for the familial cases (black) is superimposed on that for the remainder (white).

that this criterion has no value in distinguishing between genetically and environmentally determined cases of microcephaly. A comparison was also made between the same sub-groups in respect of head size; rather more "non-familial" patients have smaller heads.  $\chi^2=4.62$ , significant at between the 2 and 5 per cent. level.

### THE SIBLINGS OF MICROCEPHALIC PATIENTS

The status of the siblings of our patients is shown in Table VI. Since we wished to assess the risk of another sibling being affected, it was important to avoid choosing patients because they were known to have an affected sibling.

TABLE VI  
*Colchester Survey of 1,148 Mentally Defective Patients (Penrose, 1954)*  
*Siblings of 114 Microcephalics*

|                                                                         |    |    |    |    |    |    |     |                              |
|-------------------------------------------------------------------------|----|----|----|----|----|----|-----|------------------------------|
| Total number of patients (from index, post-mortem and admission series) | .. | .. | .. | .. | .. | .. | 114 |                              |
| Total of siblings                                                       | .. | .. | .. | .. | .. | .. | 166 |                              |
| Half siblings                                                           | .. | .. | .. | .. | .. | .. | 24  |                              |
| Miscarriages                                                            | .. | .. | .. | .. | .. | .. | 39  | (+3 potential half siblings) |
| Mentally defective siblings                                             | .. | .. | .. | .. | .. | .. | 10  |                              |
| Microcephalic siblings                                                  | .. | .. | .. | .. | .. | .. | 7   | (on measurement)             |
| Probably microcephalic                                                  | .. | .. | .. | .. | .. | .. | 2   |                              |
| Not microcephalic                                                       | .. | .. | .. | .. | .. | .. | 1   |                              |
| Deformed stillborn (included under miscarriages)                        | .. | .. | .. | .. | .. | .. | 2   |                              |
| Percentage mentally defective of total                                  | .. | .. | .. | .. | .. | .. | 6.0 |                              |

Of 4,580 siblings:

|                                    |    |    |                      |
|------------------------------------|----|----|----------------------|
| Imbecile and idiot                 | .. | .. | 164 or 3.6 per cent. |
| "Feeble-minded" imbecile and idiot | .. | .. | 431 or 9.4 per cent. |

For this analysis therefore, the material was confined to the first three groups mentioned in the previous section, that is, the indexed cases, the post-mortem series, and the series of admissions. The cases indexed as familial were not drawn upon as such, being included only if they were contained in one of the other three groups.

Every effort was made to obtain information about all the siblings. Basically, details were obtained from three sources: the social worker's history taken during a visit to the home; a history supplied by the local authority; and a questionnaire completed by the parents. Supplementary letters were written for further information to hospitals where the patient had previously been treated; to the hospital, if any, where he was born; to the general practitioner in some cases. In the case of siblings who had died, hospital records often supplied valuable information. In some cases additional visits to the home were made, or the relatives attended, bringing siblings with them in case of doubt as to microcephaly or mental deficiency. Whenever there was a question of backwardness, efforts were made to obtain head measurements of the sibling concerned.

The 114 patients considered in this connection had 166 siblings, of whom 10, or 6 per cent., were mentally defective. Of these 10, one was not microcephalic on measurement, 7 were within the microcephalic range, and the remaining 2, though not measured, appeared obviously microcephalic to observers. In one of these cases the sibling died when 25 days old. No external measurements were obtained but the brain was recovered and weighed 210 g.



against a normal average of 358 g. for the age. The head was said to be abnormal in shape and the mother complained that the baby had a hemiplegia. When admitted to hospital she was hypotonic, unable to suck, and appeared to be unconscious. In the other case which was not measured, the sibling died at 8 days and was certified at death as a case of microcephaly, being described in the notes as of the "anencephalic" type, meaning presumably that the cranium was very small. Some details of the affected siblings are set out in Table VII.

TABLE VII  
*Ten Mentally Defective Siblings of Microcephalics*

| Case No.        | Microcephalic | Spastic                                           | Epilepsy | Head Circumference (S.D. below Mean for Sex and Age) |
|-----------------|---------------|---------------------------------------------------|----------|------------------------------------------------------|
| 1 .. .. .       | —             | +                                                 | P        | 1.2                                                  |
| 2 .. .. .       | +             | Death at 8 days certified as microcephaly         |          |                                                      |
| 3 .. .. .       | +             | —                                                 | —        | 4.3                                                  |
| 4 .. .. .       | +             | Died at 25 days, hemiplegic, head and brain small |          |                                                      |
| 5 .. .. .       | +             | —                                                 | —        | 3.9                                                  |
| 6 } One Sibship | +             | +                                                 | —        | 6.6                                                  |
| 7 } .. .. .     | +             | +                                                 | —        | 5.3                                                  |
| 8 } .. .. .     | +             | +                                                 | +        | 3.3                                                  |
| 9 .. .. .       | +             | —                                                 | —        | 5.9                                                  |
| 10 .. .. .      | +             | +                                                 | +        | 3.5                                                  |

P=petit mal.

P=petit mal.

The fact that 9 out of 10 of the mentally defective siblings were microcephalic, strongly suggests genetic factors with a specific mode of operation. In order to assess the significance of the findings, it is however desirable to know the incidence of mental defect among siblings of mental defectives in general. The figures given by Penrose (1954) show an incidence of 431 "defectives" among 4,580 siblings. The figures include the "feeble-minded" and results more comparable to ours will be obtained by taking only the idiot and imbecile siblings, numbering 164, which gives a percentage of 3.6. A further difficulty in making such a comparison is that Penrose's Colchester survey of 1,148 patients includes a high proportion of feeble-minded and dull or borderline cases. If only the 653 idiot and imbecile cases in the Colchester survey (1938) are taken into account, they had 2,429 siblings whose ability was assessed, and of these 109 were considered idiots or imbeciles, a proportion of 4.5 per cent. The chief reason why more siblings are recorded in the Colchester survey than in our cases is that most of the patients in that survey were adults, whereas most of ours are young children.

In order to afford a direct comparison between the siblings of our patients with microcephaly and the general run of patients in this hospital, we have carried out a survey of the 375 siblings of 200 consecutive admissions. The number of these known to be mentally defective is 12, or 3.2 per cent. Thus, although the incidence of affected siblings is higher in the microcephalic group (6.0 per cent.), it is by no means as high as would be expected (25 per cent.), if the view of Komai and his colleagues (1955) were accepted, that the great majority of microcephalic cases is "undoubtedly of genetic origin".

It may be argued that the evidence on this point is incomplete unless the miscarriages are taken into consideration. It is known that, in our series, 2 of the babies which miscarried were malformed. It is possible that more of the

39 miscarriages might have resulted in affected infants and that they in fact miscarried because of the abnormality. This seems unlikely, however, since the proportion of miscarriages in the present series at 12 per cent. is lower than the 20 per cent. of pregnancies which is accepted as usual (Brews, 1948).

### MICROCEPHALY AND BIRTH WEIGHT

The average birth weight for 123 microcephalic children was 6 pounds 3 ounces. The mean birth weight for normal children is in the region of 7 pounds 4 ounces. The incidence of premature birth (i.e. birth weight of less than 5½ pounds) was 38 (31 per cent.), while there were 12 (10 per cent.) children with a birth weight of less than 4 pounds. The incidence of prematurity in patients in the Fountain Hospital as a whole is 29 per cent. Thus microcephaly is significantly associated with a low birth weight, as is severe mental defect in general.

Our figures did not show any significant relationship between maternal age and prematurity; between maternal age and familial incidence; or between familial incidence and prematurity.

### ASSOCIATED ABNORMALITIES

The clinical conditions associated with microcephaly are set out in Table VIII. A glance at these findings emphasizes the heterogeneity of the material and reinforces the impression that in microcephaly we are dealing with a symptom which is the end product of a variety of disease processes. A majority

TABLE VIII

#### *Clinical Findings in 131 Cases of Microcephaly*

|                         |    |    |    |    |    |    |    | No. of Cases |
|-------------------------|----|----|----|----|----|----|----|--------------|
| C.N.S. findings:        |    |    |    |    |    |    |    |              |
| Cerebral palsy          | .. | .. | .. | .. | .. | .. | .. | 86           |
| Spastic diplegia        | .. | .. | .. | .. | .. | .. | .. | 70           |
| Hemiplegia              | .. | .. | .. | .. | .. | .. | .. | 4            |
| Ataxia                  | .. | .. | .. | .. | .. | .. | .. | 2            |
| Athetosis               | .. | .. | .. | .. | .. | .. | .. | 4            |
| Atonia                  | .. | .. | .. | .. | .. | .. | .. | 3            |
| Unclassified            | .. | .. | .. | .. | .. | .. | .. | 3            |
| Epilepsy                | .. | .. | .. | .. | .. | .. | .. | 57           |
| Deaf                    | .. | .. | .. | .. | .. | .. | .. | 2            |
| Ophthalmic findings:    |    |    |    |    |    |    |    |              |
| Strabismus              | .. | .. | .. | .. | .. | .. | .. | 47           |
| Blindness               | .. | .. | .. | .. | .. | .. | .. | 26           |
| Optic atrophy           | .. | .. | .. | .. | .. | .. | .. | 18           |
| Nystagmus               | .. | .. | .. | .. | .. | .. | .. | 16           |
| Cataract                | .. | .. | .. | .. | .. | .. | .. | 11           |
| Retinal dystrophy       | .. | .. | .. | .. | .. | .. | .. | 3            |
| Microphthalmia          | .. | .. | .. | .. | .. | .. | .. | 3            |
| Retrolental fibroplasia | .. | .. | .. | .. | .. | .. | .. | 2            |
| Corneal opacity         | .. | .. | .. | .. | .. | .. | .. | 2            |
| Macular coloboma        | .. | .. | .. | .. | .. | .. | .. | 1            |
| Aniridia                | .. | .. | .. | .. | .. | .. | .. | 1            |
| Psychotic features      | .. | .. | .. | .. | .. | .. | .. | 2            |

TABLE VIII—(continued)

|                                         | No. of Cases |
|-----------------------------------------|--------------|
| Other findings:                         |              |
| Spina bifida occulta .. .. .            | 9            |
| Plagiocephaly .. .. .                   | 8            |
| Congenital abnormality of heart .. .. . | 4            |
| Pyloric stenosis .. .. .                | 3            |
| Congenital dislocation of hip .. .. .   | 3            |
| Ichthyosis .. .. .                      | 2            |
| Deformity of palate .. .. .             | 2            |
| Umbilical hernia .. .. .                | 2            |
| Arachnodactyly .. .. .                  | 2            |
| Hypospadias .. .. .                     | 1            |
| Supernumerary nipple .. .. .            | 1            |
| Hypertelorism .. .. .                   | 1            |

of the cases were suffering from cerebral palsy and, of these, nearly all had spastic diplegia, though there were 4 clear-cut hemiplegias and a few instances of the rarer athetotic, ataxic and atonic forms. As mentioned below, rhesus incompatibility does not seem to produce microcephaly, so that the classical cases of athetosis due to that cause are not included in the present group, nor do our cases which we are now considering show that relatively good preservation of intelligence which characterizes athetosis due to blood group incompatibility. The next commonest complication after cerebral palsy was epilepsy, a symptom which correlates highly with spasticity. Most of the fits were major, but some minor attacks were recorded.

The somatic findings include some which may be purely coincidental, whilst others such as the heart anomalies are probably due to the same adverse factors which produced the microcephaly.

The high incidence of ophthalmic findings is very striking. Strabismus is very common in severe mental deficiency and is attributed to brain lesions. Blindness is most commonly due to optic atrophy and represents an extension of the cerebral abnormality into the retina or optic tract. The cataract may be regarded, like the congenital heart lesions, as separate evidence of somatic damage, whilst the retrolental fibroplasia may well be a secondary complication due to the low birth weight of the microcephalic group and consequential greater risk of exposure to high oxygen concentration. The possibility should, however, be borne in mind of this lesion being also due to the same cause as that which produced the encephalopathy (Williams, 1957; Crome, 1958).

#### MICROCEPHALY AND SPASTIC DIPLEGIA

It will be seen from Table VIII that some half of the cases of microcephaly in our series suffer from spastic diplegia. Table VII shows that at least 5 of 10 mentally defective siblings of microcephalics were also spastic, including one sibling who was not microcephalic. In Table IX an attempt is made to compare 19 microcephalics with their mentally defective siblings in respect of cerebral palsy. The 19 cases were obtained by adding some of the familial cases to those derived from other sources. The numbers are too small to permit of any definite conclusions, but there is an obvious tendency for the patients with cerebral palsy to have affected siblings with the same condition. In fact in this series the combination of microcephaly and cerebral palsy occurring twice in the sibship appears six times, whilst simple microcephaly, uncomplicated by palsy, is found twice in only one sibship. The table shows also that several permutations of the three features considered are possible, suggesting that, whereas a specific



TABLE IX  
*Microcephalic Patients and Their Mentally Defective Siblings with Reference to Cerebral Palsy*

| Case No. |    |    |    |    |    |    |    | Affected Siblings |                |
|----------|----|----|----|----|----|----|----|-------------------|----------------|
| 1        | .. | .. | .. | .. | .. | .. | .. | +                 | Ø              |
| 2        | .. | .. | .. | .. | .. | .. | .. | +                 | ?              |
| 3        | .. | .. | .. | .. | .. | .. | .. | +                 | +              |
| 4        | .. | .. | .. | .. | .. | .. | .. | +                 | +              |
| 5        | .. | .. | .. | .. | .. | .. | .. | +                 | + + +          |
| 6        | .. | .. | .. | .. | .. | .. | .. | +                 | +              |
| 7        | .. | .. | .. | .. | .. | .. | .. | +                 | ?              |
| 8        | .. | .. | .. | .. | .. | .. | .. | +                 | ?              |
| 9        | .. | .. | .. | .. | .. | .. | .. | +                 | o              |
| 10       | .. | .. | .. | .. | .. | .. | .. | +                 | +              |
| 11       | .. | .. | .. | .. | .. | .. | .. | +                 | +              |
| 12       | .. | .. | .. | .. | .. | .. | .. | +                 | Ø              |
| 13       | .. | .. | .. | .. | .. | .. | .. | +                 | Ø              |
| 14       | .. | .. | .. | .. | .. | .. | .. | o                 | Ø <sup>1</sup> |
| 15       | .. | .. | .. | .. | .. | .. | .. | o                 | o              |
| 16       | .. | .. | .. | .. | .. | .. | .. | o                 | Ø              |
| 17       | .. | .. | .. | .. | .. | .. | .. | o                 | + <sup>1</sup> |
| 18       | .. | .. | .. | .. | .. | .. | .. | o                 | Ø              |
| 19       | .. | .. | .. | .. | .. | .. | .. | o                 | Ø              |

+ = microcephaly and cerebral palsy.  
o = microcephaly without cerebral palsy.  
Ø = mentally defective without microcephaly or cerebral palsy.  
<sup>1</sup> = ½ sibling.

genetic factor may produce a regular pattern as in Case 10, in other cases the genetic factor may have a variable manifestation, producing a degree of microcephaly in one sibling and mental deficiency without microcephaly in another. It will be appreciated that, since an arbitrary standard of microcephaly has been set, the differences in actual head size between siblings differently classified in this respect may sometimes be minimal.

MICROCEPHALY RESULTING FROM NON-GENETIC CAUSES

*Environmental Factors*

It is generally agreed that some cases of microcephaly are due to external causes. Murphy (1929) has been instrumental in drawing public attention to the possibility of microcephaly due to therapeutic irradiation of the mother during pregnancy and it seems likely that sufficient care is now taken to ensure that such cases occur very infrequently. Goldstein and Wexler (1931) also refer to this cause of microcephaly. From the work of Plummer (1952), who found that 7 out of 11 children born to mothers who had been exposed to the effects of the atomic explosion at Hiroshima, were microcephalic, and Yamazaki *et al.* (1954), who found 4 out of 16 microcephalics among the Nagasaki children who had been similarly exposed *in utero*, it appears that microcephaly is the commonest abnormality in humans resulting from exposure to irradiation at an early stage of development. It is to be hoped that it will be possible to prevent the recurrence of such cases in future.

*A Case of Irradiation Microcephaly*

Although the occurrence of this form of microcephaly is well recognized, it may be useful to record an additional case which occurred within recent years. A woman of 41, who had been married for many years, had no children and had never been pregnant. She was fat and she complained of severe,

persistent backache. Ankylosing spondylitis was diagnosed, and, as other treatments proved ineffective, she was given X-ray therapy on two occasions; the first time the upper part of the lumbar spine was irradiated and, on the second occasion, treatment was applied directly to the pelvis. In view of the long period of infertility and the obesity, pregnancy was not suspected at the time of the treatment. However, the last menstrual period occurred one month after the first irradiation. Cessation of the periods was attributed by the patient to the effect of the treatment and she did not mention when she attended for the second treatment, presumably in the fourth month of her pregnancy, that the periods had not occurred as usual. The estimated effective dose to the foetus was 350–400 r. spread over 13 days. The baby weighed  $2\frac{1}{2}$  pounds at birth and was microcephalic. The head circumference was 38.7 cm. at 2 years, and 40.0 cm. at 5 years. She sat up at 19 months. At the age of six years she was an imbecile with a developmental quotient of about 20. She could run about, fed herself with bread and butter, and attended the occupation centre, but had no speech. She was small for her age and had marked internal squint. The length of the skull was 17.55 cm. and the breadth 14.55 cm., cranial index 0.78 cm. The forehead was sloping. No trace of the fontanelle could be felt, but radiologically the sutures were still clearly visible (Figs. 3 and 4). The appearance of the patient did not differ from that of others with no known aetiology or those which are described as microcephalia vera. As usual in cases of microcephaly (Spitzer and Quilliam, 1958), the facial skeleton was well formed and dentition normal, in contrast with such conditions as mongolism (Spitzer and Mann, 1950). There were well-developed frontal sinuses.

#### OTHER ENVIRONMENTAL CAUSES

The role of other external factors in producing microcephaly is less well defined. Komai *et al.* (1955) take the view that the evidence for the production of microcephaly by non-genetic agents other than irradiation is not convincing.

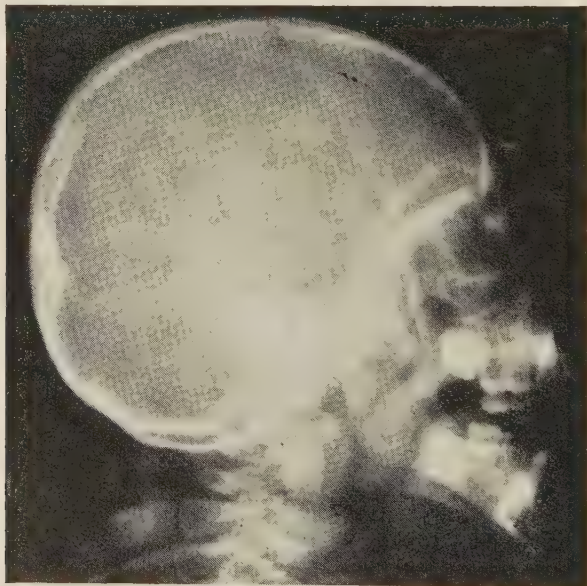


FIG. 3.—Irradiation microcephaly. Lateral view of skull at age of 6 years. Sutures still clearly visible.



FIG. 4.—Irradiation microcephaly. Front view of skull.

Böök (1953) refers to asphyxia at birth, brain infection, encephalitis, maternal rubella and some other maternal infections as possible causes, but points out that the evidence for some of these is not very soundly based. In order to permit further conclusions to be drawn on this aspect of the matter, certain known causes of intra-uterine and neonatal pathology will now be reviewed in respect of head size.

### *Rubella*

Among the case records of the Fountain Hospital, which provides for mentally defective children, there are 7 cases in which the defect was almost certainly due to maternal rubella, and a further three likely cases. Most of these were reported previously, Kirman (1955). Some data on these 10 cases are set out in Table X and Figure 5. It will be seen that, although the cranial circumference of these children is, on average, significantly less than the normal for

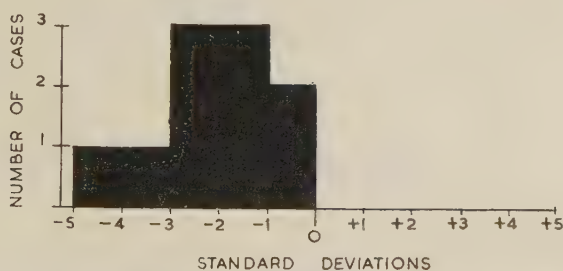


FIG. 5.—Ten cases of rubella embryopathy showing effect upon cranial circumference assessed in terms of standard deviations from the mean for age and sex.



TABLE X

*Ten Cases of Mental Defect with History of Maternal Rubella in Early Pregnancy*  
Skull Circumference (cm.)

| No.   | Sex | Admission Age | Actual | Average for Age | Less 3 S.D.     |
|-------|-----|---------------|--------|-----------------|-----------------|
| 1(?)  | M   | 4 8/12        | 47·0   | 51·8            | 47·39           |
| 2 ..  | M   | 5 11/12       | 48·1   | 52·3            | 47·45           |
| 3 ..  | M   | 7 2/12        | 52·6   | 52·7            | 48·26           |
| 4(?)  | M   | 9 6/12        | 50·0   | 52·7 (7 yrs +)  | 48·26 (7 yrs +) |
| 5 ..  | M   | 2 8/12        | 46·4   | 50·4            | 46·35           |
| 6 ..  | M   | 6 10/12       | 45·7   | 52·7            | 48·26           |
| 7 ..  | F   | 6 10/12       | 50·0   | 52·2            | 46·09           |
| 8(?)  | M   | 4             | 48·3   | 51·2            | 46·97           |
| 9 ..  | F   | 4 1/12        | 50·0   | 50·7            | 46·32           |
| 10 .. | F   | 3 5/12        | 47·0   | 49·5            | 45·45           |

Those marked (?) are in some doubt. Cases 1 and 6 lie within the microcephalic range.

the age and sex, in only two cases is the measurement more than three standard deviations less than the normal average. In other words, there were two cases of microcephaly among 10 mental defectives whose condition was probably due to rubella. Although this incidence is not high, it is important since it extends the concept of secondary microcephaly beyond the cases determined by radiation, which is all that some authorities are willing to allow. Both of the microcephalic patients had a complete rubella syndrome with bilateral cataract, deafness, congenital abnormality of the heart, and severe mental defect. In one case the mother was ill with a generalized red rash and headache during the first month of pregnancy. She did not see a doctor but a nurse told her that she had measles. In the other case it was, unfortunately, not possible to trace the mother directly, as she was in the Congo, but there was an indirect report from the local health authority which had dealt with the child in this country that the mother had had rubella during the pregnancy.

Of 52 cases of rubella embryopathy in New South Wales (Director-General, 1945), 44 showed a degree of "microcephaly" and 7 were greatly below average, but measurements are not given. Swan and his colleagues (1946) gave a series of head circumferences showing that 7 of 49 children suffering from rubella embryopathy were microcephalic as judged by the standards adopted in this paper.

### *Kernicterus*

It seems clearly established that damage to the foetus in the early stages of pregnancy can cause microcephaly. The effect of brain lesions incurred at a later stage of development on skull growth is, however, much less certain. Since the diagnosis of birth injury is always a very difficult problem, it was thought that a series of cases of kernicterus might provide a good example of the effect of a clearly recognized brain lesion occurring in the immediate neonatal period. Twenty cases of icterus gravis neonatorum were found among the patients in a mental deficiency hospital and are set out in Table XI. The first 18 of these patients were thought to be suffering from the effects of blood group incompatibility. Most of them were reported previously by Crome *et al.* (1955). In all of these cases it seemed reasonable to suppose that the icterus neonatorum was the prime or sole cause of the mental defect. In the last two patients there

TABLE XI

*The Skull Circumference in 20 Cases of Icterus Gravis Neonatorum*

|     |     |               | Skull Circumference (cm.) |                 |             |  |
|-----|-----|---------------|---------------------------|-----------------|-------------|--|
| No. | Sex | Admission Age | Actual                    | Average for Age | Less 3 S.D. |  |
| 1   | ..  | M 2 7/12      | 47·6                      | 49·8            | 45·63       |  |
| 2   | ..  | F 1 7/12      | 43·2                      | 47·0            | 43·10       |  |
| 3   | ..  | F 2 1/12      | 47·0                      | 48·0            | 44·04       |  |
| 4   | ..  | M 1 2/12      | 48·3                      | 46·8            | 42·60       |  |
| 5   | ..  | M 2 5/12      | 47·6                      | 49·8            | 45·63       |  |
| 6   | ..  | M 2 11/12     | 49·5                      | 50·4            | 46·35       |  |
| 7   | ..  | F 2 11/12     | 48·3                      | 49·5            | 45·45       |  |
| 8   | ..  | M 5 3/12      | 49·5                      | 51·8            | 47·39       |  |
| 9   | ..  | F 3 4/12      | 46·4                      | 50·1            | 45·75       |  |
| 10  | ..  | F 2 3/12      | 45·1                      | 48·8            | 44·75       |  |
| 11  | ..  | M 3 10/12     | 50·8                      | 51·2            | 46·97       |  |
| 12  | ..  | M 2 2/12      | 48·3                      | 49·1            | 44·69       |  |
| 13  | ..  | F 2 7/12      | —                         | —               | —           |  |
| 14  | ..  | M 5 3/12      | 50·8                      | 51·8            | 47·39       |  |
| 15  | ..  | F 8 0         | 48·9                      | 52·2            | 48·09       |  |
| 16  | ..  | M 5 3/12      | 52·1                      | 51·8            | 47·39       |  |
| 17  | ..  | M 1 4/12      | 47·0                      | 47·9            | 43·70       |  |
| 18  | ..  | M 2 10/12     | 48·9                      | 50·4            | 46·35       |  |
| 19  | ..  | M 3 6/12      | 50·8                      | 51·0            | 46·80       |  |
| 20  | ..  | F 4 0         | 46·4                      | 50·7            | 46·32       |  |

was also icterus gravis and a strong possibility that the brain lesion was causally related to the jaundice, though blood group incompatibility was not demonstrated. The children in this group showed a great diversity of clinical signs, and it was difficult to distinguish between mental retardation secondary to athetosis, deafness or other physical handicaps, and that ascribable more directly to damage to higher cerebral centres. Crome's finding that lesions were by no means confined to the lower centres is relevant.

It will be seen from Figure 6 that these children as a group showed marked

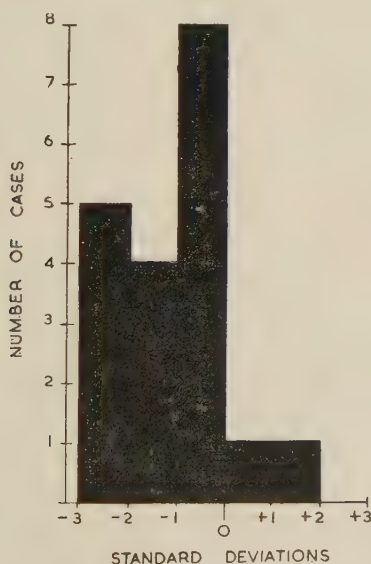


FIG. 6.—Nineteen cases of icterus gravis neonatorum showing effect upon cranial circumference assessed in terms of standard deviations from the mean for age and sex.

reduction in cranial circumference, though not to the extent of gross microcephaly. Thus, this form of neonatal brain lesion is capable of producing some retardation in cranial growth but is not commonly a cause of marked microcephaly.

### *Meningitis*

Table XII and Figure 7 show the findings in regard to head circumference in 35 cases of mental defect ascribed to meningitis. The problem of head size

TABLE XII  
*Head Sizes in 35 Cases of Meningitis*

| No. | Sex | Infection | Age at Onset | Admission Age | Skull Circumference (cm.) |                 | Less 3 S.D. |
|-----|-----|-----------|--------------|---------------|---------------------------|-----------------|-------------|
|     |     |           |              |               | Actual                    | Average for Age |             |
| 1.  | F   | T         | 13/12        | 2 8/12        | 48.2                      | 48.8            | 44.75       |
| 2.  | F   | M         | 12/12        | 4 8/12        | 55.5                      | 51.0            | 46.56       |
| 3.  | M   | I         | 4/12         | 11 7/12       | 54.6                      | 52.7            | 48.26 (7+)  |
| 4.  | M   | I         | 7/12         | 4 6/12        | 51.4                      | 51.6            | 47.25       |
| 5.  | F   | U         | 8/52         | 3 4/12        | 52.0                      | 50.1            | 45.75       |
| 6.  | F   | I         | 2/12         | 4 7/12        | 42.5                      | 51.0            | 46.56       |
| 7.  | F   | M         | 5/12         | 5 11/12       | 54.6                      | 51.7            | 47.35       |
| 8.  | F   | T         | 16/12        | 4 5/12        | 47.0                      | 51.0            | 46.56       |
| 9.  | F   | P         | 15/12        | 4 10/12       | 48.9                      | 51.2            | 46.70       |
| 10. | M   | P         | 7/12         | 2 6/12        | 48.3                      | 49.8            | 45.63       |
| 11. | F   | U         | 5/12         | 7 10/12       | 52.7                      | 52.2            | 48.29       |
| 12. | F   | T         | 18/12        | 5 5/12        | 52.0                      | 51.5            | 46.70       |
| 13. | M   | M         | 7/12         | 2 9/12        | 51.4                      | 50.4            | 46.35       |
| 14. | F   | T         | 7/12         | 2 9/12        | 47.5                      | 49.5            | 45.45       |
| 15. | F   | U         | 4/12         | 2 11/12       | 50.8                      | 49.5            | 45.45       |
| 16. | M   | U         | uncertain    | 8/12          | 43.2                      | 45.7            | 41.50       |
| 17. | F   | M         | 5/12         | 2 3/13        | 60.3                      | 48.8            | 44.04       |
| 18. | M   | T         | 18/12        | 2 6/12        | 49.5                      | 49.8            | 45.63       |
| 19. | M   | M         | 9/12         | 2 4/12        | 45.7                      | 49.8            | 45.63       |
| 20. | M   | T         | 4 6/12       | 5 3/12        | 49.5                      | 51.8            | 47.39       |
| 21. | M   | T         | 2 2/12       | 8 2/12        | 48.3                      | 52.7            | 48.26       |
| 22. | M   | T         | 10/12        | 4 8/12        | 54.6                      | 51.6            | 47.25       |
| 23. | M   | T         | 3 2/12       | 6 7/12        | 58.2                      | 52.7            | 48.29       |
| 24. | M   | P         | 6/52         | 2 6/12        | 45.7                      | 49.8            | 44.75       |
| 25. | F   | T         | uncertain    | 4 10/12       | 57.1                      | 51.2            | 46.70       |
| 26. | M   | T         | 12/12        | 5 0           | 52.0                      | 51.8            | 47.39       |
| 27. | F   | T         | 12/12        | 4 5/12        | 53.3                      | 51.0            | 46.56       |
| 28. | F   | Py        | 1/52         | 4 0           | 52.0                      | 50.7            | 46.32       |
| 29. | M   | P         | 9/12         | 1 10/12       | 49.5                      | 49.1            | 44.69       |
| 30. | F   | T         | 8/12         | 2 1/12        | 45.7                      | 48.0            | 44.04       |
| 31. | F   | P         | 6/52         | 2 5/12        | 50.2                      | 48.8            | 44.75       |
| 32. | M   | M         | 2 0          | 3 2/12        | 50.2                      | 50.4            | 46.35       |
| 33. | F   | T         | uncertain    | 9/12          | 45.7                      | 44.6            | 40.37       |
| 34. | M   | U         | 9 days       | 11/12         | 66.0                      | 46.8            | 42.60       |
| 35. | F   | T         | 2 11/12      | 3 7/12        | 50.2                      | 50.1            | 46.80       |

T = tuberculous      P = pneumococcal  
 M = meningococcal    Py = pyocyaneus  
 I = influenzal        U = unknown

after meningitis is complicated by hydrocephalus, and amongst these cases it will be seen that there are two children with an extreme degree of this condition, having a head circumference respectively 11 and 13 standard deviations greater than the average. Two other cases exceeded the average by more than three standard deviations. At the other extreme was one case within the microcephalic range with a head 5.7 standard deviations less than the average. This one case of microcephaly might have been attributed to the severe attack of influenzal meningitis which she had at the age of 2 months. Account must be taken, however, of the fact that she was premature, weighing only  $4\frac{1}{2}$  pounds at



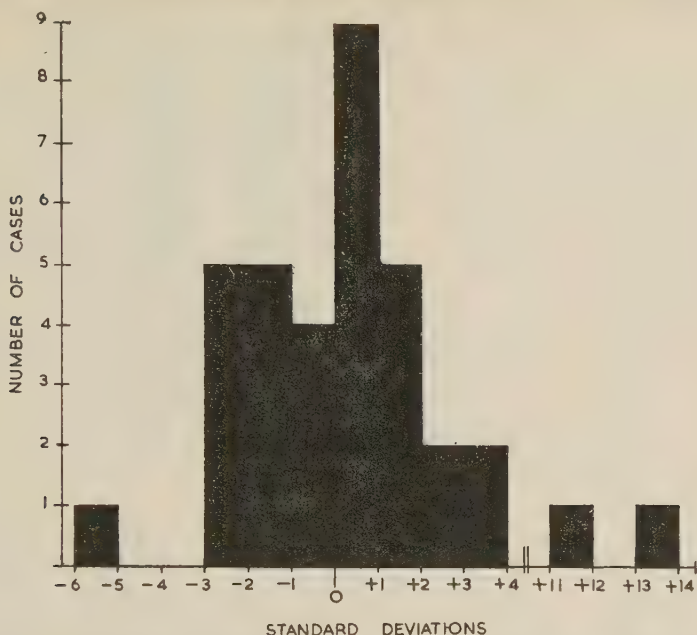


FIG. 7.—Thirty-five cases of infantile meningitis and mental defect showing cranial circumference assessed in terms of standard deviations from the mean for age and sex.

birth, with a head circumference of  $12\frac{1}{2}$  inches (31.8 cm.), which places her 2.9 standard deviations below the Vickers and Stuart mean before her illness. She also appeared to have a minor degree of retrolental fibroplasia. At 6 years she was a helpless, hemiplegic idiot, head circumference 43.2 cm. (17 inches), breadth 12.1 cm. ( $4\frac{3}{4}$  inches) and length 15.2 cm. (6 inches). She was very ill during the meningitis, collapse occurred at one stage and the cerebro-spinal fluid remained grossly abnormal for a month. In view of the early history, it cannot be stated with certainty that the small head is due to the meningitis, and it is quite possible in this, as in some other of our cases, that more than one factor is involved.

There is therefore no clear evidence in our data to incriminate meningitis as a cause of microcephaly, though its occasional operation, and likewise that of other severe illnesses soon after birth, to produce reduced head size, cannot be excluded.

#### *Evidence from Twins*

Brandon *et al.* (1959) give an account of two pairs of twins, one of each pair being microcephalic, the other quite normal in intelligence and head size. In both cases the twins were identical. It was thought that environmental factors operating during pregnancy were responsible for the microcephaly, though birth trauma could not be entirely excluded as a factor. This is a further piece of evidence in favour of the occurrence of "acquired" microcephaly. Hinden (1956) recorded a similar case.

#### *Mongolism*

The unknown factors responsible for this syndrome are a common cause of smallheadedness. As shown in Table XIII, children with mongolism tend to have small heads for their age. Of the 30 cases which figure in this table, 10

TABLE XIII  
*Head Sizes in 30 Cases of Mongolism*

|     |     |               | Skull Circumference (cm.) |                 |             |  |  |
|-----|-----|---------------|---------------------------|-----------------|-------------|--|--|
| No. | Sex | Admission Age | Actual                    | Average for Age | Less 3 S.D. |  |  |
| 1   | ..  | F 1 3/12      | 45.7                      | 45.6            | 41.94       |  |  |
| 2   | ..  | F 8/12        | 41.9                      | 44.6            | 40.37       |  |  |
| 3   | ..  | F 3 10/12     | 45.7                      | 50.7            | 46.32       |  |  |
| 4   | ..  | F 3 10/12     | 48.3                      | 50.7            | 46.32       |  |  |
| 5   | ..  | F 3           | 43.8                      | 49.5            | 45.45       |  |  |
| 6   | ..  | M 1 6/12      | 43.8                      | 47.9            | 43.70       |  |  |
| 7   | ..  | M 11/12       | 43.2                      | 46.8            | 42.60       |  |  |
| 8   | ..  | M 6 3/12      | 46.4                      | 52.3            | 48.26       |  |  |
| 9   | ..  | M 1 1/12      | 44.5                      | 46.8            | 42.60       |  |  |
| 10  | ..  | M 1 11/12     | 45.7                      | 49.1            | 44.69       |  |  |
| 11  | ..  | M 4 6/12      | 45.1                      | 51.6            | 47.25       |  |  |
| 12  | ..  | M 3 1/12      | 47.0                      | 50.4            | 46.35       |  |  |
| 13  | ..  | M 1 8/12      | 47.0                      | 47.9            | 43.70       |  |  |
| 14  | ..  | M 2 9/12      | 50.2                      | 50.4            | 45.63       |  |  |
| 15  | ..  | M 3 6/12      | 47.0                      | 51.0            | 46.80       |  |  |
| 16  | ..  | M 3 8/12      | 46.4                      | 51.0            | 46.80       |  |  |
| 17  | ..  | M 1 11/12     | 43.2                      | 49.1            | 44.69       |  |  |
| 18  | ..  | M 1 9/12      | 45.7                      | 49.1            | 43.70       |  |  |
| 19  | ..  | M 3 11/12     | 48.9                      | 51.2            | 46.97       |  |  |
| 20  | ..  | M 3 7/12      | 44.5                      | 51.0            | 46.80       |  |  |
| 21  | ..  | M 1 8/12      | 41.9                      | 47.9            | 43.70       |  |  |
| 22  | ..  | M 3 10/12     | 50.8                      | 51.2            | 46.97       |  |  |
| 23  | ..  | M 3 10/12     | 45.1                      | 51.2            | 46.97       |  |  |
| 24  | ..  | M 4 11/12     | 49.5                      | 51.8            | 47.39       |  |  |
| 25  | ..  | M 11/12       | 45.7                      | 46.8            | 42.60       |  |  |
| 26  | ..  | M 5 5/12      | 50.2                      | 51.8            | 47.39       |  |  |
| 27  | ..  | M 3 8/12      | 47.0                      | 51.0            | 46.80       |  |  |
| 28  | ..  | M 4 1/12      | 45.7                      | 51.2            | 46.97       |  |  |
| 29  | ..  | M 2 8/12      | 50.8                      | 49.8            | 45.63       |  |  |
| 30  | ..  | M 3 11/12     | 48.9                      | 51.2            | 46.97       |  |  |

could be classed as microcephalic using the criteria outlined above. They are distinguished from ordinary cases of microcephaly by the fact that there is a very general dystrophy affecting almost all the organs, whilst in microcephaly there is a tendency for the abnormality to be localized in a very striking manner to the cranium and its contents (see Figs. 3 and 4). Another distinguishing feature is the relative brachycephaly of the children with mongolism. It is known that the factors which produce mongolism are active in the early part of pregnancy and probably exert their main effect about the sixth week. In this respect, i.e. in the time relationship, they may be similar to the factors producing ordinary cases of microcephaly; on the other hand, so far as the retardation of head growth is concerned, the factors producing mongolism are less potent since it is rare to find cases of severe microcephaly in mongolism. It will be seen from Figure 8 that all the cases shown as microcephalic in the table can be classed as examples of a medium degree of severity. In view of the fact that low birth weight is noted very commonly among children with mongolism—29 per cent. were classed as premature in our series at the Fountain Hospital, that is to say, they had a birth weight of less than  $5\frac{1}{2}$  pounds—it was thought possible that those children who fell into the microcephalic range for skull circumference would also be those who had small birth weights. However, no clear relationship between these two measurements emerges. Out of 8 of the microcephalic mongolian children whose birth weight was recorded, only two were

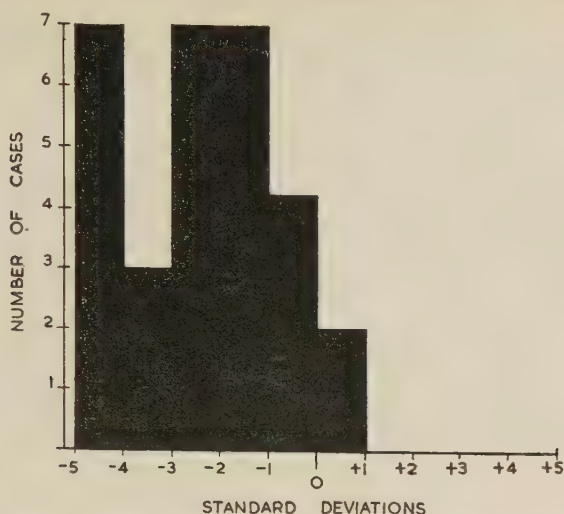


FIG. 8.—Thirty cases of mongolism showing cranial circumference assessed in terms of standard deviations from the mean for age and sex.

premature (as defined), which is the expected number if there were no relationship.

#### MATERNAL AGE

It was found that the average age of 133 mothers at the birth of their microcephalic child was 26·8 years. This was two years younger than the mothers of 100 consecutive mental defectives who were not microcephalic or mongols. This difference is significant at below the 1 per cent. level. For comparison the national average is 27·8 (based on Registrar-General, 1953).

#### INTELLIGENCE IN MICROCEPHALY

The following notes briefly summarize the findings in regard to mental capacity:

Intelligence test results were available on 108 microcephalic patients, and, although testing is difficult when dealing with children as backward as this, and many have developmental quotients rather than intelligence quotients, they are a guide to the abilities of these children. They have an average I.Q. of 11, with an S.D. of 12. The highest I.Q. found was 59, which was obtained by an adult. A large number of children had an I.Q. below 1. The distribution of intelligence is shown in Table XIV. Where more than one assessment has been made, there seems to have been a drop in I.Q. over the years. This may be

TABLE XIV

#### *Distribution of intelligence in microcephaly*

| 0-4 | 5-9 | 10-14 | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | Total |
|-----|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 44  | 18  | 19    | 7     | 7     | 3     | 4     | 2     | 0     | 1     | 1     | 2     | =108  |

due to the fact that these children develop relatively better physically than mentally and that the developmental type of test used when they are young gives higher scores than a test demanding intellectual ability. On the other hand, it may reflect a real tendency towards deterioration. Head size tended to fall off with intelligence.  $\chi^2=7\cdot75$ . This is significant at the 1 per cent. level.



The average I.Q. of the "familial" group is 12.3 and for the "non-familial" is 10.4. These are not significantly different. The average I.Q. of the 32 children who died was 5.4.

Since these patients were all selected as mental defectives, they may not fully represent the intelligence of people with small heads. It may be that there are some persons within the microcephalic range who would achieve rather better scores than those shown. A closer relationship between intelligence and head size might be expected, until account is taken of the diversity of brain pathology in these cases and the fact that there is often a gross defect in quality as well as quantity of brain substance.

There is no real evidence to support the view often put forward that microcephalics have some sort of special temperament or that they are especially active, show "quick, furtive movements" or are friendly and fond of music. It is well nigh impossible to support similar claims with objective evidence even in the case of such a clear-cut entity as mongolism (Marrs, 1955).

#### ANATOMICAL FINDINGS

It is not proposed here to give a detailed account of the neuropathology of microcephaly. Crome (Hilliard and Kirman, 1957) has discussed the matter in general and in relation to the related abnormalities of microgyria (1952) and pachygyria (1956). A more recent study by the same author in preparation showed that of 176 otherwise unclassified mental defectives, 106 had brains which weighed less than 80 per cent. of the mean for the age. Most of these brains showed a variety of structural abnormalities apart from the smallness.

Among those patients in our series who had microcephalic relatives, the brains were available for study post-mortem in 6 cases. There was a further case where the parents were first cousins. As shown in Table 15, the findings

TABLE XV  
*Brain in Familial Microcephaly*

| Case No. | Family Data                     | Weight*     | State of Brain                                                          |
|----------|---------------------------------|-------------|-------------------------------------------------------------------------|
| 1.       | Stillborn microcephalic sibling | 110 (1,351) | Shallow sulci, with surface mantle and ectopic grey matter within.      |
| 2.       | Microcephalic sibling           | 740 (1,275) | Microgyria.                                                             |
| 3.       | Microcephalic sibling           | 210 (358)   | Massive destruction of white and grey matter, resembles leucodystrophy. |
| 4.       | Microcephalic cousin            | 834 (1,237) | Shrunk with gliosis.                                                    |
| 5.       | Microcephalic cousin            | 912 (1,237) | Both brains shrunk with gliosis especially occipitally.                 |
| 6.       | Microcephalic cousin            | 826 (1,253) |                                                                         |
| 7.       | Parents first cousins           | 282 (950)   | Shrunk with gliosis.                                                    |

\* Figures in parenthesis are mean brain weights for age.

were very diverse and support the view that, even in the genetically determined cases of microcephaly, the material is not homogeneous and that we are dealing with more than one factor and pathological process.

Cases 1 and 2 show an error which must have been determined very early in development, whilst in Cases 4-7 the early stages probably proceeded fairly normally, arrest occurring later in pregnancy. Case 3 showed a remarkable

picture of a highly destructive process with some resemblance to leucodystrophy, though this group of conditions is not usually associated with microcephaly. Cases 5 and 6 were maternal cousins and showed what appeared to be a specific type of lesion.

Penrose (1954) states that "The brain in true microcephaly is extremely small and may weigh less than 1,000 g. but it need not show pathological lesions. The cortical convolution pattern is much simplified." Wallin (1956) makes a similar statement. None of our familial cases conform to this description. It may be argued that this is because none of them are cases of "true" microcephaly. We prefer to advocate the abandonment of the use of this term in favour of an attempt to subdivide microcephaly in terms of aetiological factors, environmental or genetic, clinical features, e.g. presence or absence of palsy, and nature of brain lesion.

### CONCLUSION

Microcephaly is a purely descriptive term and includes conditions with varying aetiology and pathology. If the phenomenon of microcephaly is to be investigated objectively, it is desirable that it should be defined in some manner such as that suggested, i.e. three standard deviations below the mean of head circumference for the age and sex.

It is not possible within the category of microcephaly as defined above to separate off a group of cases with "true microcephaly", since the criteria used to make this differentiation do not correspond to any real difference between the possibly "genetic" group of cases and the others.

Microcephaly can be determined by environmental factors and has been recorded in one of uniovular twins. Such factors include ionizing radiation; infection during pregnancy, notably rubella; probably a variety of other adverse factors in the intra-uterine environment; possibly also severe brain damage during or soon after birth. Such a severe illness as kernicterus does not, however, seem commonly to produce microcephaly, perhaps because of the selective nature of the brain lesions. Patients suffering from certain classified syndromes may also fall within the microcephalic range, e.g. in mongolism, acrocephaly, phenylketonuria and sucroseria.

The evidence suggests that there may be more than one genetically determined form of the condition produced by different genetic factors.

Twenty per cent. of mentally defective children in our series, mongolism excluded, are microcephalic, as defined above. The death rate among the microcephalics is higher than among other mental defectives.

The high familial incidence in published material on microcephaly may be partially explained by selection of cases in favour of those with a familial incidence. The evidence from our data suggests that only a minority of cases are genetically determined.

The risk of another mentally defective child being born to a mother who has already had one microcephalic offspring is of the order of 6 per cent., as compared with a corresponding figure of 3.2 per cent. for other defectives in our hospital; the odds are heavily in favour of such a child being also microcephalic.

More than half the cases of microcephaly suffer from cerebral palsy, which usually takes the form of spastic diplegia. Epilepsy is common and there are often multiple lesions including eye abnormalities. Our material shows more evidence of the familial incidence of the form of microcephaly with spastic

diplegia than of the uncomplicated form. In a number of cases a mentally defective sibling was not microcephalic. This suggests the possibility that similar pathogenic factors may produce varying manifestations and that consequent reduction in head size may not always reach the microcephalic level.

#### SUMMARY

The concept of microcephaly and of "true" microcephaly is critically reviewed. Cases with a head circumference more than 3 standard deviations below the mean for age and sex are accepted as microcephaly. One case presumed due to irradiation of the mother during pregnancy, 2 thought due to maternal rubella are described. One of each of two pairs of uniovular twins were also found to have microcephaly. No instances were recorded among 20 cases of icterus gravis neonatorum. One-third of children with mongolism fall into the microcephalic range. Of 100 admissions to the Fountain Hospital, mainly idiots and imbeciles, 26 were in the microcephalic range, of which 6 had mongolism. In 64 deaths at the hospital, 34 were of microcephalic size, including 13 with mongolism. In a series of 102 clinical cases, there were two sets of consanguineous parents, 9 instances of mentally defective siblings, and 9 instances of mental defect among other close relatives. There was no significant difference between the cranial index of the "familial" group and the others. A series of 114 unselected cases of microcephaly had 166 siblings, of whom 10 were mentally defective; of these, 9 were microcephalic. In 131 cases examined clinically, 86 had cerebral palsy, of which 70 had spastic diplegia. Fifty-seven had epilepsy.

Nineteen cases of microcephaly were compared with their mentally defective siblings in respect of cerebral palsy. Thirteen of the 19 had cerebral palsy and their sibling was similarly affected in 6 cases. Among the defective siblings of the 6 microcephalics without cerebral palsy, there was one with this condition. In 7 cases, the mentally defective sibling was not microcephalic, in 9 cases it was.

Maternal age was significantly lower than in the case of other defectives, mongols excluded.

One hundred and eight cases of microcephaly had an average intelligence quotient of 11, with a standard deviation of 12, range 0-59. A relationship was found between head size and intelligence, significant at the 1 per cent. level.

The morbid anatomy was very varied, 7 of the brains from "familial" cases were examined, 2 showed lesions dating from early, and 4 from late, pregnancy, whilst one had an atypical leucodystrophy.

It was concluded that only a minority of our cases were primarily due to specific genetic factors, the nature of the environmental factors involved being usually unknown. There are probably at least two specific genetic factors causing microcephaly. The risk of another child being affected is 6 per cent. in our series. There is as yet no clinical basis for distinction between genetic and non-genetic cases apart from family history.

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# LIVER DAMAGE IN ADDICTIVE ALCOHOLICS

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ALMOST 125 years ago Addison (1836) suggested the existence of a causal relationship between alcoholism and cirrhosis of the liver and more than 100 years ago Rokitsansky noted accumulation of fat as the earliest effect on the liver of over-indulgence in alcohol (cited from Connor, 1938). Though the relative importance of infective hepatitis and alcoholism as aetiological agents in liver cirrhosis may vary a great deal in different countries, "alcohol and infective hepatitis are at present the only two unequivocal aetiological factors" (Annotation, *Brit. Med. J.*, 1957). It is usually accepted that over-indulgence in alcoholic drinks often produces liver dysfunction—maybe in an indirect manner—which though reversible at first, tends to become irreversible as over-indulgence is continued and prolonged (Levy, Cunliff, Walton and Healey, 1954). The terminal phases are characterized by cirrhosis, hypertrophic at first and then contracted, with ascites and eventual death. When individuals whose drinking habits lead them to this state need hospital treatment, they seem to find their way into general hospitals rather than into mental hospitals. Among them may be alcoholics of the type described by a World Health Organization Expert Committee as "habitual symptomatic excessive drinkers" (W.H.O. Rep., 1952) or "non-addictive alcoholics", and those excessive drinkers whose alcoholism manifests itself in their "inability to stop" continual daily drinking in the face of dangerous consequences (W.H.O. Rep., 1955).

Yet liver cirrhosis is a relatively late complication of alcoholism and supervenes in only a certain proportion of alcoholics. Haggard and Jellinek (1950) estimate that liver cirrhosis does not occur in more than about 8 per cent. of "chronic alcoholics". On the other hand, according to these authors fatty infiltration of the liver constitutes the most common physical disturbance of chronic alcoholism, occurring in 75 to 80 per cent. of chronic alcoholics.

In this country, alcoholic patients entering mental hospitals taking a special interest in alcoholism hardly ever show clinical evidence of liver damage. Their

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main problems associated with their alcoholic habits are psychological or social, rather than physical or somatic disturbances. Almost all these patients belong to the type of alcoholic termed "alcohol addicts" characterized by "loss of control" over their alcohol intake once they have started to drink on a certain occasion. These people do not usually suffer from marked physical disturbances but often they have long-standing psychological difficulties—feelings of inadequacy, inability to cope with tension and frustration, etc.—from which they have sought to escape by taking alcoholic drinks. In contrast to the non-addictive alcoholic who "can avoid drunken behaviour whenever the social situation requires it" (W.H.O. Rep., 1952), the addictive alcoholic has usually run into serious difficulties in the sphere of his social adjustment, at work, at home, etc., which often precipitate his hospital admission.

The admission of a steady stream of addictive alcoholics, who in spite of a long-continued history of over-indulgence in alcohol coupled with gross neglect of their food intake showed little clinical evidence of physical damage, raised the question whether the laboratory could detect abnormalities in liver function and in vitamin B<sub>1</sub> balance in these people. Vitamin B deficiency may be precipitated in alcoholics by various factors, such as dietary inadequacy, defective absorption and possibly an increased need for thiamine caused by the high calorie value of alcohol. The series of investigations here reported was therefore undertaken.

#### CASE MATERIAL

The patients were addictive alcoholics newly admitted to Warlingham Park Hospital.

The investigation began early in 1953 and although it was continued for a number of years, only the results obtained in 1953 and 1954 are now analysed. At first, blood analyses only were done, but early in 1954 the bromsulphalein clearance test described by Goodman (1952) was included. The patients examined in 1953 had had vitamin B<sub>1</sub> as part of their routine treatment on admission and before the laboratory tests; those examined in 1954 had not had any treatment before the tests were carried out. This, together with sex differences, divided the patients into groups, as shown in Table I.

TABLE I  
*Distribution by Age, Sex and Year of Admission of 118 Alcoholics*

| Year | Group         |    | Number | Age Range | Mean | S.D. |
|------|---------------|----|--------|-----------|------|------|
| 1953 | Males I ..    | .. | 47     | 27-68     | 46.1 | 9.9  |
| 1954 | Males II ..   | .. | 42     | 23-64     | 41.9 | 10.1 |
|      | Total         | .. | 89     | 23-68     | 44.1 | 10.2 |
| 1953 | Females I ..  | .. | 17     | 38-75     | 52.0 | 9.2  |
| 1954 | Females II .. | .. | 12     | 41-66     | 53.2 | 7.5  |
|      | Total         | .. | 29     | 38-75     | 52.5 | 8.6  |

Both female groups were older than both male groups, the differences being statistically significant ( $p < .05$  in each case). The age difference between the two male groups was also statistically significant. This suggests that men seek treatment earlier or start drinking younger than women, and that as time went



on men were seeking treatment at an earlier stage. From the clinical point of view, however, all the 118 patients were a homogeneous group. Almost all were in good physical condition. None had clinically detectable cirrhosis or ascites, although the liver was enlarged in 15 patients. One patient—a woman—had had at some unascertained time a liver biopsy and had been told that she had “a 50 per cent. cirrhosis”. Our tests showed that she had liver damage but not cirrhosis. About 20 patients had mild symptoms or signs of polyneuritis; one elderly woman had beri-beri, two others showed mild signs of pellagra. There were two cases of Korsakoff’s syndrome. All were “alcoholics” as defined by the Alcoholism Sub-Committee of the W.H.O. Expert Committee (W.H.O. Rep., 1952), almost all were “alcohol addicts” with “loss of control”. Socially, they were mostly of the professional and middle classes and all had long histories, on the average 10–15 years, of alcoholic over-indulgence which had eventually brought them in need of special treatment. About four-fifths had neglected their food intake for several years (on the average 4–5 years) before admission.

### TESTS AND CRITERIA

Table II gives the tests used and the criteria for assessing abnormality.

TABLE II

*Investigation of Alcoholics: Biochemical Tests Used and Criteria of Abnormality*

| Tests                              |    |    |    |    |                    | Abnormal if                |
|------------------------------------|----|----|----|----|--------------------|----------------------------|
| Serum:                             |    |    |    |    |                    |                            |
| Van den Bergh, direct and indirect | .. | .. | .. | .. | ..                 | Positive                   |
| Bilirubin                          | .. | .. | .. | .. | ..                 | >0.5 mg. per cent.         |
| Proteins: Total                    | .. | .. | .. | .. | ..                 | <6.0 g. per cent.          |
| Albumen                            | .. | .. | .. | .. | ..                 | <4.0 g. per cent.          |
| Globulin                           | .. | .. | .. | .. | ..                 | >2.5 g. per cent.          |
| A/G ratio                          | .. | .. | .. | .. | ..                 | <1.5                       |
| Electrophoresis: Albumen           | .. | .. | .. | .. | ..                 | Low                        |
|                                    |    |    |    |    | $\alpha$ -Globulin | Raised                     |
|                                    |    |    |    |    | $\beta$ -Globulin  | Raised                     |
|                                    |    |    |    |    | $\gamma$ -Globulin | Raised                     |
| Alkaline phosphatase               | .. | .. | .. | .. | ..                 | <5 or >10                  |
| Cholesterol: Total                 | .. | .. | .. | .. | ..                 | <150 or >250 mg. per cent. |
| Free/Ester ratio                   | .. | .. | .. | .. | ..                 | >0.5                       |
| Takata-Ara test                    | .. | .. | .. | .. | ..                 | Positive                   |
| Cholinesterase                     | .. | .. | .. | .. | ..                 | <50 units                  |
| Bromsulphalein clearance test      | .. | .. | .. | .. | ..                 | <4 ml./kg./min.            |
| Blood:                             |    |    |    |    |                    |                            |
| Urea                               | .. | .. | .. | .. | ..                 | >45 mg. per cent.          |
| Coccarboxylase                     | .. | .. | .. | .. | ..                 | <5 $\mu$ g./100 ml.        |
| Pyruvate                           | .. | .. | .. | .. | ..                 | >1.5 mg./100 ml.           |

### Techniques

With the exception of the B.S.P. clearance test (Goodman, 1952), which was newly adopted for this investigation, all the techniques were those in daily routine use in our laboratory.

Proteins were estimated by the biuret method. Globulins were separated in 26.7 per cent. ammonium sulphate.

Electrophoresis was done in the Antweiler micro-Tiselius apparatus on only 25 sera, partly owing to limitations of time and partly because it was our usual practice not to carry out electrophoresis when the serum globulin was less than 2.5 g. per cent. The Takata-Ara reaction was carried out by the technique of Ragins (1934–35) but the increasing use of electrophoresis gradually led to the abandonment of this test which was not showing many positive results.

Other techniques were as follows:

Alkaline phosphatase: King and Armstrong (1934) whose normal range was adopted;  
 Cholesterol, total, free and ester: a modification of the method of Schoenheimer and Sperry (1934);  
 Cholinesterase: in Warburg manometers at 30° C. using acetylcholine as substrate; one unit is the amount of esterase liberating 1  $\mu$ l. of CO<sub>2</sub>/ml. of serum/minute;  
 Urea: Archer and Robb (1925);  
 Cocarboxylase: Kay and Murfitt (1956);  
 Pyruvate: Friedemann and Haugen (1943).

#### *Collection of Blood*

Puncture of an arm vein was effected with minimal stasis to distend the vein and then, whilst blood was flowing freely in the vein, 30–40 ml. of blood were collected and distributed in appropriate receptacles. Most of the males and females of Group I walked to the hospital laboratory for venepuncture about 2–3 hours after breakfast. All the patients of Group II were bled in bed after overnight fast, prior to carrying out the B.S.P. clearance test.

### RESULTS

Excluding for the time being abnormalities in urea, cocarboxylase and pyruvate results, abnormalities in one or more tests were found in 86 (72·8 per cent.) of the 118 patients. These were distributed among the groups as follows:

TABLE III

*Investigation of Alcoholics: Number in Each Group Who Showed Abnormalities*

|             |    |    |    | All Cases | With Abnormality | Per cent. |
|-------------|----|----|----|-----------|------------------|-----------|
| Males I     | .. | .. | .. | 47        | 29               | 61·7      |
| Males II    | .. | .. | .. | 42        | 33               | 78·6      |
|             |    |    |    | —         | —                | —         |
| All males   | .. | .. | .. | 89        | 62               | 69·7      |
|             |    |    |    | —         | —                | —         |
| Females I   | .. | .. | .. | 17        | 13               | 76·5      |
| Females II  | .. | .. | .. | 12        | 11               | 91·7      |
|             |    |    |    | —         | —                | —         |
| All females | .. | .. | .. | 29        | 24               | 82·8      |
|             |    |    |    | —         | —                | —         |
| All cases   | .. | .. | .. | 118       | 86               | 72·8      |
|             |    |    |    | —         | —                | —         |

There is an obvious tendency for the members of both sexes in Group II to show more evidence of abnormality than those in Group I.

The distribution of abnormal results according to tests as well as groups is shown in Table IV.

With the exception of the Takata-Ara reaction, all the tests used appeared to be able to detect substantial proportions of abnormal values which can be attributed to hepatic dysfunction. No single test detected all the patients likely to show abnormalities. Even the B.S.P. clearance test gave low values in only 17 (31·5 per cent.) of the 54 patients tested by it. Of the same patients, 28 (51·9 per cent.) showed abnormalities in their proteins, 19 (35·2 per cent.) in their phosphatase, and in all, 44 (81·5 per cent.) showed some abnormality or other. The presence of a raised  $\beta$ -globulin in 48 per cent. of the 25 sera tested by electrophoresis suggests that this abnormality, which is associated with a toxic disturbance of the liver, is likely to be the most frequent evidence of reversible hepatic damage associated with alcoholism. Every test detected abnormalities in some patients who showed no abnormalities by the others. All the tests in the battery are therefore necessary. They seem to be concerned with different aspects of hepatic function, each of which may react differently to alcoholic onslaughts.

TABLE IV  
*Investigation of Alcoholics: Summary of Results of Tests*  
 Numbers of Cases Showing Abnormalities

| Type of Abnormality          | Males  |        | Females |        | Total    | As<br>Per<br>cent.<br>of<br>Cases<br>Tested |
|------------------------------|--------|--------|---------|--------|----------|---------------------------------------------|
|                              | I      | II     | I       | II     |          |                                             |
| Hyperbilirubinaemia ..       | 2      | 3      | 1       | 0      | 6        | 5.1                                         |
| Proteins:                    |        |        |         |        |          |                                             |
| Low total ..                 | 1      | 9      | 2       | 5      | 17       | 14.4                                        |
| Low albumen ..               | 8      | 10     | 3       | 8      | 29       | 24.6                                        |
| High globulin ..             | 11     | 7      | 7       | 3      | 28       | 23.7                                        |
| Raised $\alpha$ -globulin .. | 0 (10) | 1 (5)  | 0 (6)   | 1 (4)  | 2 (25)   | 8.0                                         |
| Raised $\beta$ -globulin ..  | 1 (10) | 4 (5)  | 3 (6)   | 4 (4)  | 12 (25)  | 48.0                                        |
| Raised $\gamma$ -globulin .. | 1 (10) | 2 (5)  | 1 (6)   | 0 (4)  | 4 (25)   | 16.0                                        |
| Phosphatase:                 |        |        |         |        |          |                                             |
| Low ..                       | 8      | 12     | 1       | 1      | 22       | 18.6                                        |
| High ..                      | 1      | 4      | 2       | 2      | 9        | 7.6                                         |
| Cholesterol:                 |        |        |         |        |          |                                             |
| Low total ..                 | 14     | 4      | 0       | 0      | 18       | 15.2                                        |
| Raised F/E ..                | 6      | 4      | 0       | 0      | 10       | 8.5                                         |
| Cholinesterase:              |        |        |         |        |          |                                             |
| Low ..                       | 8 (38) | 4 (41) | 1 (12)  | 1 (12) | 14 (103) | 13.6                                        |
| T.A.R. positive ..           | 1 (45) | 0 (15) | 3 (15)  | —      | 4 (75)   | 5.3                                         |
| B.S.P. clearance:            |        |        |         |        |          |                                             |
| Low ..                       | —      | 11     | —       | 6      | 17 (54)  | 31.5                                        |
| Number of cases in groups    | 47     | 42     | 17      | 12     | 118      |                                             |

Tests not applied indicated by —.

Numbers in parentheses are the numbers to whom tests were applied, when less than group total.

It is of further interest to examine the distribution of the number of abnormalities shown by each case in the groups. This is done in Table V.

TABLE V  
*Investigation of Alcoholics: Distribution of Number of Abnormalities Found per Case According to Groups*

| Groups             | Number of Abnormalities Per Case |      |      |      |     |     |     |     | Total<br>Cases |
|--------------------|----------------------------------|------|------|------|-----|-----|-----|-----|----------------|
|                    | 0                                | 1    | 2    | 3    | 4   | 5   | 6   | 7   |                |
| Males I cases ..   | 18                               | 12   | 9    | 4    | 2   | 1   | —   | 1   | 47             |
| Males II cases ..  | 9                                | 13   | 10   | 4    | 4   | —   | 2   | —   | 42             |
| Females I cases .. | 4                                | 6    | 4    | 2    | 1   | —   | —   | —   | 17             |
| Females II cases   | 1                                | 2    | 3    | 4    | —   | 2   | —   | —   | 12             |
| All groups: cases  | 32                               | 33   | 26   | 14   | 7   | 3   | 2   | 1   | 118            |
| As percentages ..  | 27.2                             | 28.0 | 22.0 | 11.8 | 5.9 | 2.5 | 1.7 | 0.9 | 100            |

There is an evident tendency for the maximum number of cases in the different cells to shift towards the right in passing from Group I to Group II and from males to females, suggesting that there was more evidence of hepatic dysfunction in Group II than in Group I, and in females than in males. The latter results corresponded with the clinical findings. There were usually more



marked bodily disturbances in the female patients, who also more often showed clinical evidence of peripheral neuritis and of hypovitaminosis.

Taking all the 118 cases together, a distribution curve can be plotted as in Figure 1.

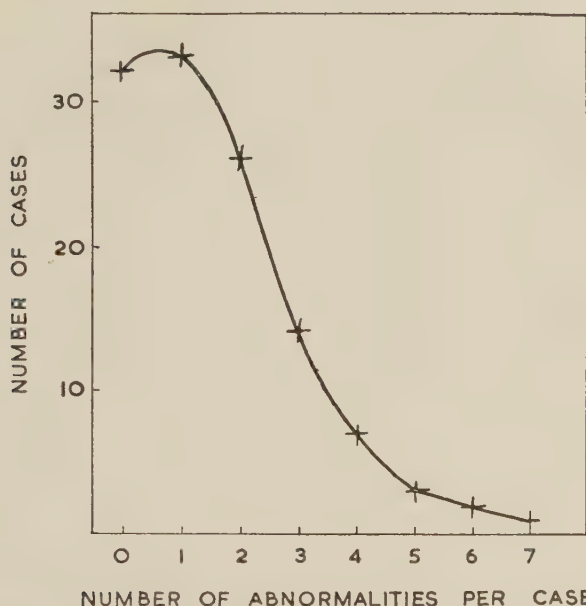


FIG. 1.—Investigation of alcoholics: distribution curve of cases showing different numbers of abnormalities.

The resemblance of this curve to that of natural distribution suggests that the selection of criteria is approximately correct. Re-examination of criteria showed that the omission of some could give a true curve of natural distribution. We are to conclude, therefore, that alcoholics of the clinical type studied, having little or no clinical evidence of hepatic dysfunction, nevertheless do show a high proportion of abnormal results in the battery of tests used, and are to be regarded, therefore, as having liver dysfunction in varying degrees.

This conclusion is supported by the results obtained in re-examinations after abstinence from alcohol by, and treatment of the patient. Twenty-five patients who showed abnormalities at the first testing gave improved or even normal results at the second. From this we may infer that their liver damage was of the reversible type. These findings correspond to those of Leevy *et al.* (1954) who noted a disappearance of all evidence of liver disease in patients with fatty livers on discontinuance of drinking and maintenance of a good dietary intake.

Two men of Group I came to necropsy. Both showed fatty changes in their liver, but no cirrhosis. Their blood chemistry when admitted was as follows:

(a) Aged 68. Van den Bergh reaction and serum bilirubin, normal; serum proteins: total 6.4 g. per cent., albumen 3.7 g. per cent., globulin 2.7 g. per cent., A/G ratio 1.4/1; T.A.R. negative; serum cholesterol: total 135 mg. per cent., free 40 mg. per cent., ester 95 mg. per cent., F/E ratio 1/2.4; serum alkaline phosphatase 4 units; serum cholinesterase 34 units; urea 36 mg. per cent. The cholesterol, albumen, phosphatase and cholinesterase were all low and consistent with liver dysfunction of reversible type. There was no anaemia. Death occurred 11 weeks after the test.

(b) Aged 57. Van den Bergh and serum bilirubin, normal; serum proteins: total 6.4 g. per cent., albumen 3.8 g. per cent., globulin 2.6 g. per cent., A/G ratio 1.5/1; T.A.R. negative;

electrophoretic pattern normal; serum cholesterol: total 164 mg. per cent., free 41 mg. per cent., ester 123 mg. per cent., F/E ratio 1/3; serum alkaline phosphatase 5 units; serum cholinesterase 43 units; urea 16 mg. per cent. Six weeks later, although the albumen and cholinesterase had improved, the cholesterol and phosphatase had fallen. Death occurred ten months after the first test.

### COCARBOXYLASE AND PYRUVATE RESULTS

The patients of Group I of both sexes had had vitamin B<sub>1</sub> treatment when their blood was examined. Of the men, 42 were tested and none showed an abnormally low cocarboxylase value. Indeed, a number showed abnormally high values—evidence of more than adequate medication. Of 15 Group I women examined, 4 had abnormally low cocarboxylase values. In one case thiamine deficiency was confirmed by an abnormal response of the blood pyruvate to glucose administration. In spite of an adequate cocarboxylase level, 14 of 46 men and 5 of 16 women all of Group I had high blood pyruvate levels, suggesting that the mild exercise they had taken to reach the laboratory had overtaxed their not fully-recovered cocarboxylase mechanism.

The patients of Group II had not had vitamin B<sub>1</sub> treatment and were all bled fasting and in bed. All had normal pyruvates. Two men and 5 women had abnormally low cocarboxylase values.

These results indicate that this type of alcoholic is prone to add thiamine deficiency to his liver dysfunction.

### SUMMARY

The results of the battery of tests used in examining the blood of a group of 118 alcoholics, male and female, coming for treatment in a mental hospital, indicate that in spite of the absence of clinical signs, alcoholics are prone to show abnormal blood chemistry indicative of hepatic dysfunction, and in some cases of thiamine deficiency. To detect abnormalities adequately a battery of tests such as the one used is essential.

### ADDENDUM

Further to the results discussed above, the tests have been carried out as a routine procedure in more than 350 patients admitted until 1957 to Warlingham Park Hospital Alcoholic Unit. The results in this larger series confirm essentially the above findings. Similarly, blood pyruvate tests in a total of 380 patients and cocarboxylase tests in about 250 patients bear out the conclusions derived from the smaller initial sample. The overall impression gained from these investigations, and from the results of tests for urobilinogen and bilirubin in urine, is that of a frequent disturbance of blood and urine chemistry related to liver function and vitamin B<sub>1</sub> blood level. This is despite the absence of clinical evidence of abnormalities, and of a rapid improvement in a considerable proportion of patients after a relatively short period of abstinence from alcohol and a vitamin-supplemented full diet. All these observations once more bear out the necessity of the diagnosis and treatment of alcoholism at an earlier stage, before the development of clinical evidence of physical complications.

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# SOME CRITICISMS OF FACTOR ANALYSIS WITH SUGGESTIONS FOR ALTERNATIVE METHODS

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## I.—INTRODUCTION

It is well known that a factor analysis may be carried out in various ways; the subjective elements involved make it by no means clear that two people beginning with the same data will arrive at the same conclusions. Furthermore, not enough attention has been paid to the confirmation of factors revealed in one analysis by repetition of the tests on another sample from a similar or different population.

Besides this, very often the data which are factor analysed are not suitable for this type of treatment, and the value of a piece of research is often obscured by the inappropriate use of the technique, and by a failure to clarify the purpose of the statistical analysis. In a recent paper Storms (1958) has shown how the technique of discriminant functions may reveal more clearly than factor analysis differences in personality structure in different psychoneurotic groups.

The purpose of this paper is twofold. In the first place an attempt is made to elucidate some of the sources of confusion and circularities of argument which arise when a factor analysis is carried out. Attention is also drawn to the need for a detailed description of the sample before an interpretation of the factors extracted can be made. Alternative approaches are then discussed. In some circumstances a more satisfactory procedure is to make a hypothesis regarding the presence of certain factors, and to test this hypothesis; in others, other techniques may be appropriate, and these are discussed and compared. Lastly the use of a new technique is exemplified in relation to a particular piece of research.

## II.—NAMING AND ORTHOGONALITY OF FACTORS

It has frequently been pointed out (for example by Burt (1940) and Thomson (1950)) that a factor is a weighted mean of the scores of the tests included in the battery. In spite of this, in naming a factor it is often implied that the measure obtained has some absolute meaning. This cannot be the case unless the tests included in the battery are really representative of all the possible tests of the ability or trait which gives the factor its name. The name given to a factor may, in fact, conceal its true nature, and little is gained in being told that "the factor X has been identified", if, on inspection of the tests loaded with this factor, it appears that the author has greatly extended or limited or even changed the attributes usually ascribed to the quality X.

Furthermore, the definition of a factor may be considerably strained owing to a prior assumption that any factors which are present are orthogonal, or alternatively, that any orthogonal factors found with high loadings are psychologically meaningful. Now, if an examination of the tests *after* the factor



analysis suggests that they measure certain characteristics in common, then a similar examination *before* factor analysis should reveal the same possibility. A hypothesis can therefore be made to this effect which can be tested in the manner outlined in Section IV. Other factors can also be postulated and their significance and mutual orthogonality tested.

It is interesting to examine Eysenck's (1954, chap. 4) study of political affiliation in the light of this criticism. In this study, which is based on the answers to an opinion survey, the author claims to have discovered two fundamental dimensions on which opinions are based; one he names Radicalism-Conservatism, and the other, which is orthogonal to the first, he names Toughminded-Tenderminded. Now, examination of those opinions which have high loadings on the first factor suggest that it has been correctly named, and it seems unlikely that many people will disagree with what is there regarded as "radical" and "conservative". However, the axis orthogonal to it is not so easily recognizable and it is not at all obvious that it measures a "nameable" characteristic. Because a few statements at one end of the scale appear to fit in with William James' (1907) concept of "Toughmindedness" and a few at the other end fit in with the opposite idea of "Tendermindedness", the whole scale has been labelled with these names. As a result of this, some of the statements, particularly those relating to morality and religion, seem to be classified as "tenderminded" whereas in the everyday use of these terms they might well be regarded either as unclassifiable as they stand, or else as "toughminded". It seems worth noting that the qualities listed by James under the two headings were ascribed to the two main schools of philosophers existing at that time, and their meanings can only be interpreted in this context. For one group we have Rationalistic, Intellectualistic, Idealistic, Optimistic, Religious, etc. (tenderminded), and for the other, Empiricist, Sensationalistic, Pessimistic, Irreligious, etc. (toughminded); in the context of James' writing it becomes clear that these adjectives have a considerably narrower meaning than is usual. Whether or not one agrees with the meaning ascribed by Eysenck to the new dimension is clearly a matter of opinion, but the method of arriving at the factor cannot be regarded as satisfactory. An examination of the meaning of each statement should enable one to make a hypothesis regarding the extent to which it measures "tendermindedness" or "toughmindedness", and the significance of the dimension could then be tested, and also its orthogonality to "Radical-Conservatism".

### III.—POPULATION

A fact which is often ignored is that a change in the variation of the population by selection affects the correlation coefficients, which in turn affect the factor loadings. It is unlikely that a "g" factor will be discovered in a highly intelligent group of subjects, for the emergence of a factor implies variation on that factor in the group tested. Thus if a "neurosis" factor is found in a group it implies that some members of the group are more neurotic than others, and, on the other hand, if this factor is not revealed it may mean that either the whole group is neurotic or that none of them is.

Secondly, the "significance" of a factor is often interpreted in terms of the proportion of the overall variance accounted for by the factor. If a large number of irrelevant tests are included in the battery the proportion contributed by a particular factor is reduced; conversely, if only tests which are known to be highly correlated are included, the factors which emerge will account for a

high proportion of the variance. This has been pointed out by Babington Smith (1950, section 9). Thus, every time a factor is revealed, or not revealed in an analysis an interpretation can only be made in terms of (a) the variation in the population sampled, which should be reported, and (b) the actual tests used.

There is another source of trouble which arises when instead of dealing with a random sample from one population we have several groups whose means differ significantly on some of the test scores. If this is the case, a correlation coefficient calculated over all the people is a mixture of "between groups" and "within groups" correlations, and is impossible to interpret as it stands. Figures 1 and 2 show how the inclusion of groups which differ may obscure the meaning of the correlation coefficient.

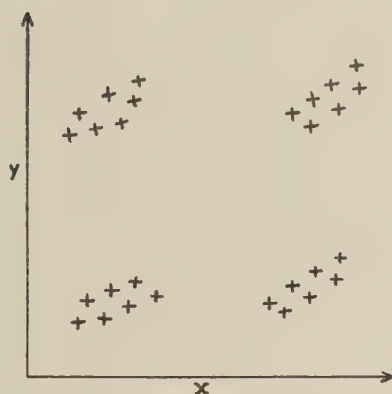


FIG. 1

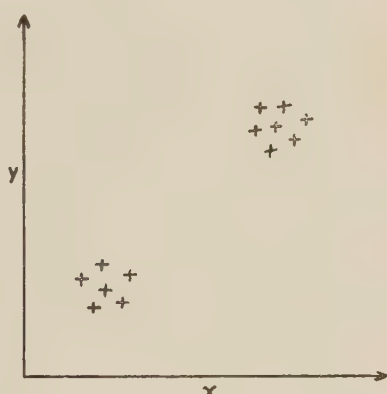


FIG. 2

In Figure 1 there is a positive correlation between the two variables within each group, but the group means are so placed that the overall correlation would be very low, and no one factor could account for most of the variance. In Figure 2, on the other hand, there is no correlation within the groups, but since the means of the two groups differ significantly an overall positive correlation would be found. In this case a factor would emerge which would probably be named by the quality distinguishing the two groups. This factor would account for nearly all the variation, since variation along the line joining the groups is large compared with that perpendicular to it. But the loadings cannot be interpreted in the usual way, nor a test of significance applied. For one of the assumptions underlying a factor analysis is that in the population studied each variable is normally distributed, and this is clearly not the case if several differing groups are included. This type of situation can probably be dealt with best by the discriminant function technique discussed in the next section. The loadings obtained from a factor analysis may be roughly related to those obtained from the use of a discriminant function, but there is no justification for carrying out the factor analysis.

Reference may again be made here to Eysenck's (1954) study. The sample investigated consisted of groups from the four main political parties, and many of the statements were such that the proportions agreeing with them differed significantly between the groups. This is therefore comparable with the situation illustrated in Figure 2, and care should be taken in attempting to interpret the factor loadings except in a very rough way. This could perhaps account for the fact that correlations calculated between the two factors *within* groups are consistently and significantly negative (Eysenck, op. cit., p. 135).

## IV.—ALTERNATIVE APPROACHES

In this section three possible alternative approaches are discussed, which may be appropriate in various circumstances. Each one appears to the author more objective than factor analysis, and more susceptible to tests of significance.

*(a) Analysis of Variance*

The existence of a factor implies that people vary significantly in their amounts of this factor; the method outlined here is based on this argument. A more detailed discussion is given in a paper entitled "Analysis of variance as an alternative to factor analysis" (Creasy, 1957).

This approach is essentially different from factor analysis, as it requires the research worker to postulate initially which factors are present in the tests used, and to what degree. The need for careful construction of a test battery has, indeed, been stressed by Guilford (1952), who points out that the initial planning should emphasize the formation of hypotheses as to what factors are likely to be found. It should be possible from examination of the tests, or from the results of a previous factor analysis, to postulate the "loading" of each test on each factor on either a 3- or 5-point scale, or merely as "present" or "absent". A measure of each person's "amount" of this factor is then the weighted sum of the test scores, weighted with the postulated factor loadings. This can be obtained for each factor and the variation between people's scores calculated.

The statistical analysis entails breaking down the overall variation between people on all the tests into components due to variation between people on the different factors postulated and residual variation. It is then possible to test the significance of these components compared with the residual variation as in an analysis of variance. If it is required to test whether the factors are orthogonal to each other this can also be done. More details can be obtained from the above mentioned paper where some examples are given and comparisons made with factor analysis. The algebra given there reveals an interesting relationship between the analysis of variance components and the correlation coefficients between the tests. (This is illustrated in the example in the following section.) It is also shown that there is very little loss of accuracy if "crude" loadings are used in place of loadings with two significant figures. If the battery of tests is balanced so that each factor occurs equally often with every other factor, the amount of computation is considerably less than that involved in a factor analysis; in any case the labour is to some extent reduced.

The advantage of this method is that it avoids some of the unsatisfactory features of factor analysis. Any elements of subjectivity involved in naming the factors can be clearly stated at the outset when the factors are postulated; furthermore, the significance and orthogonality of the factors can be tested in a satisfactory manner.

Lawley (1958) has described a method of estimation of loadings in a factor analysis where it can be initially postulated that certain loadings are zero. This method gives "best" loadings under these assumptions and is in a sense halfway between the analysis of variance approach, where all loadings are postulated, and factor analysis where all loadings are estimated. The disadvantages of the method are that as estimates are obtained by iteration the method becomes very unwieldy if more than three factors are postulated and no test of significance is available.



### (b) *Discriminant Function*

Suppose we have two groups of people that are known from general and perhaps subjective considerations to differ in respect to a quality. Then the construction of a battery of objective tests related to this quality may enable us to assign a further individual to one or other of the groups. The problem then arises of the best way to make use of the test scores to achieve this purpose. For example, suppose the quality is "neuroticism" and we have a group of "normals" and a group of "neurotics" diagnosed on the basis of a psychiatric interview. It may be that a series of tests could be devised which differentiated to some extent between the two groups. We require a method of combining the test scores in order to give a criterion for deciding from which category a new individual probably comes. The combination which gives the minimum number of errors of allocation is that obtained by the use of Fisher's (1948) technique of "discriminant function". If the requirements of normality and equality of variance in the groups have been satisfied, this will result in a weighted sum of the test scores, which gives the best discrimination (in a mathematical sense) between the groups. In the above example this weighted sum could be regarded as a measure of neuroticism. Such an approach helps to emphasize the fact that we are not necessarily dealing with a "factor" in any absolute sense, but are merely making the best use of the data available; measures of the main characteristics of neuroticism may, in fact, have been omitted from the battery. This situation is similar to that illustrated in Figure 2, where with only two tests, it can be seen to be reasonable to measure the distance along the line joining the two groups in order to decide to which group an individual is closer. In his study of the "neurotic dimension" Eysenck (1947) appears to recognize this situation when he "rotates to a criterion", and his result is probably fairly close to that which would be obtained using a discriminant function. However, the latter is more justifiable mathematically, more objective, and incidentally involves less computation. In a re-analysis of some data first analysed by Hildebrand (1958), Storms (1958) has clearly shown that a discriminant function can pick out the tests which discriminate groups of psychoneurotics more successfully than a factor analysis.

### (c) *Arbitrary Scoring*

An individual's measure of a factor is essentially a weighted sum of his test scores. If these weights are postulated, as in (a) above, we can obtain for each person a "postulated" measure which, depending on the weights chosen, will be more or less reasonable. If the purpose of a piece of research is simply to show that two groups differ in respect of this factor it is sufficient to show that the means of the postulated measures differ significantly by a t-test. This method of arbitrary weighting will not give the most sensitive test of difference between the groups, which is that discussed in (b) above, but it may be the most appropriate test in the circumstances and will certainly be easier to calculate.

## V.—ANALYSIS OF VARIANCE (EXAMPLE)

In a recent (unpublished) study by Dr. G. A. Foulds and Mr. T. M. Caine an attempt has been made to group questions on the M.M.P.I. which measure hostility into five classes, three of which refer to "Extrapunitive" and two to "Intropunitive" hostility. There are thus five measures for each person, which will be expected to intercorrelate to some extent. The question arises whether the correlations are sufficiently large to suggest there is one underlying factor

of hostility, and secondly whether there is another "factor" which gives a measure on a possible "Extrapunitive-Intropunitive" dimension.

If a general factor is present, it can be shown that a very close approximation to its value for each person is given by his average score on all the tests. The significance of the factor is tested by seeing if variation between these averages is significantly large compared with variation between the individual test scores, within each person. This is equivalent (Creasy, 1957) to testing the significance of the average of the correlation coefficients, i.e. to testing  $F = \{1 + (n-1)\bar{r}\} / (1 - \bar{r})$  as an  $F$  with  $\{(p-1), (n-1)(p-1)\}$  degrees of freedom where  $n$  is the number of tests,  $p$  the number of people tested and  $\bar{r}$  the average of the  $n(n-1)/2$  correlations. The test is only approximate if  $p < 40$ , and tends to over-estimate significance.

Now suppose we postulate an Extrapunitive hostility factor, present in the first three tests, and absent in the last two. The difference in the means of the two sets will give a measure of a person's "Extrapunitive" score, over and above his average hostility. If variation in these differences is significant, it suggests this second classification of the tests "means something" and two measures or dimensions are necessary to represent a person's "hostility position" relative to the others. The test of significance turns out to be expressible in terms of correlation coefficients, and compares the average of the correlations *within* the two sets with the correlations *between* the two sets. This is illustrated below. For details of the formulae the reader is referred to Creasy (op. cit.).

Scores were obtained from several groups of people, of which only two will be discussed here, a group of 20 "Normal" women and a group of 20 "Normal" men. (The tests of significance are therefore only approximate.) The average correlations are given in Table I. The analysis of variance takes the form shown in Table II (see op. cit.).

TABLE I

|                                              |             |    |    | Women | Men                           |
|----------------------------------------------|-------------|----|----|-------|-------------------------------|
| Average (of 10)                              | $\bar{r}$   | .. | .. | .286  | .519                          |
| Average extrapunitive                        | $\bar{r}_1$ | .. | .. | .476  | .427                          |
| Intropunitive                                | $\bar{r}_2$ | .. | .. | .470  | .484                          |
| Average extrapunitive $\times$ intropunitive |             | .. | .. | .160  | .571                          |
| $F = \frac{1+4\bar{r}}{1-\bar{r}}$           | ..          | .. | .. | 3.00  | 6.40 (both significant at 1%) |

TABLE II

| Source           | d.f. | Mean Square                           | Women Mean Square | F    | Men Mean Square | F    |
|------------------|------|---------------------------------------|-------------------|------|-----------------|------|
| General factor   | 19   | $1+4\bar{r}$                          | 2.14              | 4.06 | 3.08            | 5.60 |
| Second factor .. | 19   | $1-4\bar{r}+2\bar{r}_1+\bar{r}_2$     | 1.28              | 2.42 | .26             | .47  |
| Residual ..      | 57   | $\frac{1}{3}(3-2\bar{r}_1-\bar{r}_2)$ | .53               |      | .55             |      |

It can be seen that the first and second factors for women are significant; this means that two measures are necessary to represent a person's hostility "position" relative to the group. These may be, for example, the overall average score and the difference "Extrapunitive-Intropunitive", or simply the Extrapunitive and the Intropunitive scores separately. For the men, on the other hand, the second factor is not significant, the Extrapunitive and Intropunitive scores in fact correlate fairly highly with each other (.57) which suggests that

they do not measure different things and that the overall average score is sufficient to describe a person's hostility measure. These conclusions refer, of course, to variation within the group, and say nothing about the measures to use in a comparison of groups.

## VI.—CONCLUSIONS

The technique of factor analysis involves so many subjective elements that a piece of research summarized by a table of factor loadings is almost impossible to appreciate, even when details of tests, population, etc., are given, and these are frequently omitted. Alternative methods are available and are discussed in Section IV of this paper.

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# THE CLINICAL USE OF STILBOESTROL FOR SUPPRESSION OF SEXUAL BEHAVIOUR OF CHRONICALLY ILL MALE PSYCHIATRIC PATIENTS

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In view of the significant role the sexual instinct plays in psychiatric illness, it is surprising that there are in the literature so few reports of attempts to suppress male sexual behaviour by the direct method of modifying the physiological basis of sexual activity by oestrogen therapy. Dunn (2, 3) established that administration of stilboestrol could result in marked reduction of male libido and sexual behaviour. He treated two non-psychotic hypersexual patients and, apart from the clinical effects, observed gynaecomastia, histological evidence of reversible testicular degeneration, and depressed urinary androgen excretion. Hamburger (6) later demonstrated in one case that oestradiol administration produced the same degree of urinary androgen excretion as did actual surgical castration of the same patient. Thus, present evidence indicates that oestrogen therapy produces in the male what is, in effect, a reversible chemical castration.

To our knowledge, Foote (4), Golla and Hodge (5), and Sands (9) are the only other authors to report on this subject in the English literature. The authors of earlier studies obtained reduction of libido in all their subjects, but Sands, whose series of 27 patients is the largest, observed absence of response in two of his subjects. Because information about this use of oestrogens is evidently scanty and not entirely conclusive, we undertook to study the subject at the Verdun Protestant Hospital. In the present report the chief emphasis is upon the results of a controlled study of the administration of stilboestrol to fifteen patients with psychiatric illness of long standing. There has been no previous report of this use of the drug in such patients, nor has any such previous study been controlled.

## METHOD

The controlled study was conducted in an eight-ward building housing approximately 360 chronically ill male psychiatric patients. The patients for the study were primarily selected by the chief attendants of the various wards. The basis of selection was the patients' regularly observable sexual behaviour, which was either deviant or socially disturbing. The period of observation extended over three eight-week periods from December, 1957, to May, 1958: (I) eight weeks of preliminary observation, (II) eight weeks when approximately half the patients (chosen at random) received stilboestrol and the other half placebo, and (III) eight weeks when the medication and placebo, as given during the previous period, were reversed. Clinical observation was carried out by the ward attendants and the head nurse of the building. The attendants' daily observations were recorded on simple rating scale, assessing general ward conduct with regard to features disturbing to the ward, and the specific sexual

activity. Also noted were physical complaints, whether the patient was taking his medication, and weight (once weekly). These observations were summarized in weekly discussions with the head nurse.

During period I the author interviewed all the patients. He inquired after their general welfare, chief pre-occupations, and attitudes towards sexual matters, and also carried out a slightly modified Verdun Projective Battery (7, 8)\* and a draw-a-person test. The interview was repeated in the same form between five and eight weeks after beginning period II; it was not repeated a third time, as no significant changes were observed in the second series of interviews. Apart from this the author's contact with the patients was intentionally minimal; he saw them approximately once weekly on the wards, and seldom conversed with them on these occasions. The objective was to produce as little change as possible in the patients' routine.

Seven of the fifteen patients under study were on drugs other than stilboestrol (chiefly phenothiazine derivatives). The doctors in charge of these patients knew of their inclusion in the series, and were asked to keep other medications constant if possible, but to feel free to make changes if definitely indicated. If the administration of other drugs seems pertinent, note of it is made in the case summaries below.

Stilboestrol and the placebo were administered identically in white capsules in a single daily dose. The initial dose of the drug was 2.5 mg. daily. In some instances, as noted in the case summaries, the dose was changed after four weeks' therapy, the final range of dosage being from one to ten mg. daily. When dosage was changed, or when there was a change-over between drug and placebo, medications were merely interchanged in their respective containers. Only the author knew of such changes.

Electroencephalograms were done on two patients both before starting the drug and while on stilboestrol.

During the initial period of observation two patients were dropped from the series because they were not regularly manifesting abnormal sexual activity. Observation was later discontinued on two other subjects; one had carcinoma of the lip which was adversely affecting his general health while he was on stilboestrol; the second, whose clinical status is extremely variable ordinarily, had such marked vacillations of behaviour that it was felt that the intrusion of other factors made him an unsuitable subject for such a study. After these changes, the total number of patients in the series was 15.

## RESULTS

The observations made on the 15 patients in the study are here summarized. Significant changes in weight and any occurrence of side-effects are noted.

### *A. Suppression of Sexual Behaviour with General Behaviour Unchanged or Improved*

#### 1. Hebephrenic schizophrenia, 37, fourteen years in hospital, masturbation.

A very manneristic man of small build. Typically he can be seen carrying on an animated, unintelligible conversation with himself, complete with jerky, monkey-like gestures and changes of facial expression, with one hand in his trousers' pocket stimulating his genitals. During the period of observation he was observed masturbating in the bathroom about twice weekly. On stilboestrol

\* This is a three-part scored test, consisting of a multiple-choice Rorschach and two word-association lists, one scored for response-time and the other for conformity of response.

(up to 5 mg. daily) he rapidly developed gynaecomastia and some anorexia, and was not observed to be masturbating. Nor did he stimulate his genital region, though he continued to keep his hand in his pocket. This change was associated with a mild reduction in his general level of activity. The marked decrease in sexual behaviour continued throughout the following period on placebo. He was not on any other medication.

2. Simple schizophrenia, 57, in hospital 42 years, masturbation.

A sullen man who occasionally has outbursts of aggressive behaviour. This man was included in the study because he could almost always be seen with one hand inside his trousers stimulating his genitals, and could frequently be observed masturbating openly. It was believed that he also frequently masturbated at night. He had some tendency to hide his masturbation from the staff. On stilboestrol (up to 5 mg. daily) after about one month's therapy, his behaviour definitely changed. It became unusual to see him with a hand inside his trousers, he was not observed masturbating, and his general bearing became timid rather than latently hostile. Instead of sitting about by himself he spent more time with the other patients, and began to show an interest in television. A few weeks after stopping stilboestrol, perhaps in relation to being transferred to another ward at this time, he became disturbed. No sexual activity had reappeared. He gained 10 lb. while on the drug. He was on no other medication until after he was transferred.

3. Catatonic schizophrenia, 39, sixteen years in hospital, homosexual.

A quiet, seclusive individual, who four years prior to the study had a bilateral frontal leucotomy which served to abolish frequent outbursts of violently aggressive behaviour. He was involved in homosexual activities, including communal masturbation, with about ten other patients on his ward. There was no change during the placebo period, but this activity disappeared while he was on stilboestrol. A complicating factor in this case is that he was transferred to another ward soon after he was started on the drug. However, there was such a marked change in his sexual activity that the effect was thought to be significant. He gained 14 lb. on the drug. He was on no other medication.

4. Senile psychosis, 77, five years in hospital, masturbation.

A genial old man whose character is well preserved in spite of memory defect and a marked tendency to confabulate. He masturbated when allowed to go to bed during the day. There was some variability of this activity during the period of observation and while on placebo, but after being on stilboestrol for about a month he no longer masturbated when permitted to go to bed during the day. He was not on any other medication.

5. Simple schizophrenia, 32, eighteen years in hospital, masturbation and exhibitionism.

A dull, mute, apathetic man of simian habitus, who had a bilateral frontal leucotomy in 1955. While on placebo there was no change, but after one month on stilboestrol he developed gynaecomastia and his sexual behaviour decreased markedly. While on stilboestrol his daily dose of chlorpromazine was decreased from 600 to 400 mg., and he became somewhat less lethargic.

6. Simple schizophrenia, 46, three years in hospital, masturbation.

A detached, deteriorated schizophrenic in only superficial contact with his surroundings, whose frequent, uninhibited masturbation was one of the chief factors prompting his commitment. After about one month on stilboestrol a marked reduction in the frequency of his masturbation was noted. There had been no change while he received placebo.



*B. No Definite Change in Sexual or General Behaviour*

## 7. Schizophrenia, 30, four years in hospital, masturbation.

The present state of this patient, who is in relatively good contact with his social environment, is characterized by untidiness and inactivity, with lack of insight. There were difficulties in obtaining a consistent and objective account of his activities, as there was a change of ward attendants during the study; he had a good relationship with the first attendant, to whom he would report his masturbatory activity, but this was not so with the attendant who followed. An additional problem was that at about the time stilboestrol was started, a ward activity programme, to which he responded, was also begun. At any rate, during the control period he was observed masturbating once or twice a week, and at times reported nocturnal masturbation to the attendant. While on stilboestrol (up to 5 mg. daily) he associated during the day with student nurses participating in the ward programme, and was not observed openly masturbating. However, it was thought that he was concealing himself to masturbate. During the ensuing placebo period his behaviour continued to be oriented towards the student nurses. EEGs done before and during the period of drug administration were not appreciably different. He developed a degree of anorexia while on stilboestrol and lost 15 lb.; this weight loss persisted while he was on placebo.

## 8. Mongoloid, 38, four years in hospital, masturbation and homosexuality.

This man carried on in a childish and irritable way during the period of observation, he had numerous superficial staphylococcal skin lesions at this time, and did not appear to be in good health. During the drug period (up to 5 mg. daily) he developed anorexia, vomiting, and gynaecomastia, and the daily dose was reduced to 1 mg. His weight did not change on stilboestrol, but decreased 15 lb. on placebo. Throughout the entire period of study his sexual behaviour fluctuated to a certain extent, but the general pattern did not change: he usually had one hand inside his trousers stimulating the anogenital region, and was intermittently the passive object of other patients' homosexual advances. During the latter part of the drug period the skin pustules cleared, and there was considerable improvement in his general health and more spontaneity in his behaviour.

## 9. Mongoloid, 28, nine years in hospital, masturbation.

This patient was included in the study because he constantly has a hand inside his trousers stimulating the anogenital region, and easily forms passive relationships with other patients on the ward. When on stilboestrol (up to 5 mg. daily) he soon developed anorexia and vomited after every meal. The dose was reduced to 1 mg. daily, and after he had regained his usual health, his sexual behaviour resumed its usual pattern. While on the drug he lost about 10 lb., which he did not regain on placebo.

## 10. Catatonic schizophrenia, 21, four years in hospital, homosexuality.

A silly, negativistic half-breed Indian, who has a homosexual attachment to patient 11. EEGs done before and during the course of stilboestrol therapy (up to 5 mg. daily) revealed an increase in slow wave activity while on the drug. However, neither his general behaviour, nor homosexual activity, changed significantly on the drug.

## 11. Mental deficiency without psychosis, three years in hospital, homosexuality.

A dull, untidy man with a vapid smile, who looks older than his age. He

was included in the study because of a homosexual relationship with patient 10. There was no significant change in his behaviour during the study.

12. Psychosis secondary to cerebral anoxia resulting from cardiac arrest during operation, 25, nine years in hospital, masturbation and homosexuality.

This demented young man, whose general level of function is that of an imbecile (I.Q. 45), and who also has mild athetosis, masturbates frequently and is also the object of other patients' homosexual advances. During the entire period of study there was no change reported in his sexual activity; for some time he was on 5 mg. stilboestrol a day. During the period on drug he had a skin rash which disappeared.

13. Imbecile, 43, three years in hospital, masturbation.

A cheerful little man who clings to the attending staff. During the period on placebo he developed an ill-defined illness which lasted several weeks, and which was associated with a marked decrease in his sexual behaviour. Masturbation returned just before he was started on stilboestrol, and then disappeared while he was on the drug. It is probable that he did have a response to the drug, but we do not feel such a conclusion is justified by our data.

### *C. Deterioration of General and/or Sexual Behaviour*

14. Schizophrenia, 29, four years in hospital, exhibitionism.

A tense, withdrawn young man who responds quickly to psychological testing. The patient was included in the study because of compulsive exhibiting, which was in evidence whenever female members of the staff came on to the ward. Prior to treatment with stilboestrol this behaviour could be avoided with little fuss by secluding him when female staff members were expected. However, it was interesting to see that on stilboestrol, although he did not at these times have an erection as he would have had previously, his desire to exhibit was much more pronounced and difficult to control, and at times he would become quite desperate.

15. Simple schizophrenia, 30, fourteen years in hospital, masturbation.

Before leucotomy (January, 1957) this man was considered one of the most dangerous patients in the hospital. His behaviour prior to the drug study, however, was relatively calm, though he generally seemed tense and pre-occupied, and frequently sought reassurance from the staff. The patient himself is much concerned over his frequent masturbation. Because of the method of observation, it is difficult to ascertain what effect the drug had on him. It is certain that he became aware that the new medication was directed at his sexual activity. A decline in masturbation was noted while he was on placebo, but this returned to its usual frequency while still on placebo. Then on stilboestrol masturbation again disappeared, and he became more disturbed than he had been since his leucotomy: he was very tense, attempted suicide, and required large doses of sedatives to control him. There were marked fluctuations in weight throughout, bearing no relation to whether he was on stilboestrol. He developed gynaecomastia on the drug.

Apart from these patients, we also observed three others:

16. Catatonic schizophrenia, 43, twenty-three years in hospital.

A tense man, this patient was included in the study to see if stilboestrol would have any effect on his pronounced tendency to become destructive when he was permitted to be free on the ward. While still on placebo he had three grand mal convulsions. There was no previous history of seizures. When

placed on dilatin and phenobarbital not only his seizures, but also his aggressive behaviour, stopped. Observations as part of the present study were discontinued.

17. Paranoid schizophrenia, 68, twenty years in hospital.

This man has a characteristic habit which he can be observed practising almost continuously throughout the day: he sits by himself tightly rolling bits of paper into six-inch-long sticks, which he calls his "secrétaires". It was thought that this activity might represent a masturbation substitute, so he was included in the study. There was no change in his behaviour until towards the end of the drug period (5 mg. daily): for one day he did not roll his papers. After this he continued just as before.

18. Pathological personality, anti-social (post-leucotomy), 29, re-admitted during the present study.

Study of this man's behaviour was not done in the manner of the experimental design, in that he knew he was taking stilboestrol in order to suppress his masturbation and homosexual behaviour, and did not have a period on placebo. The drug was apparently completely successful in suppressing his libido, and after the drug had been stopped for a few weeks, sexual behaviour started to return.

### DISCUSSION

The design of this study was such as to keep changes in the field of observation to a minimum by having the ward personnel make all the day-to-day observation, while the author had little contact with the patients. This scheme was quite successful, though undoubtedly one or two of the subjects became aware that they were objects of observation, and that the new medication was directed at their sexual activity. An important defect in the study is that the bulk of the data was provided by ward attendants with little training in recording clinical observations. However, in most instances the patients were well known to them, and although subtler changes may have escaped notice, marked changes in behaviour were certainly reported.

There are two other features which might be criticized: (a) Since the effects of stilboestrol do not subside for a variable number of weeks after cessation of its administration, the placebo effect was not adequately tested in the group who received the drug first and placebo second. This problem could have been averted by prolonging the study. (b) The author, who was aware of the schedule of therapy in each case, also compiled the recorded observations, and may have brought some bias to the results. We think that it is evident from the case reports that analysis of the observations was performed critically; little weight was given to transient or ill-defined changes in behaviour, so that any bias would operate in the direction of decreasing the number of responses to the drug.

Only six of the fifteen patients in the series showed a definite decrease in sexual activity without any undesirable changes in behaviour. This proportion is at variance with other reports, but is consistent with previous experience at the Verdun Protestant Hospital. In a similar, but uncontrolled study done in 1955 in this hospital it was found that eight of eighteen patients treated with stilboestrol had a reduction of sexual activity. Three patients (Nos. 5, 6, 12) who received the drug both in 1955 and during the present study, showed essentially the same response on each occasion. Earlier investigators obtained quite uniform reduction of sexual behaviour, but Sands, treating a group of 27 psychopathic, schizophrenic, and neurotic patients, found that two of his



patients manifested no change in such activity. Apart from the different techniques of study, there are two other factors to be considered in accounting for our markedly different proportion of responses: (a) Age and chronicity of illness were probably important factors resulting in a relative fixity in our patients' patterns of sexual behaviour. The average age of our patients was 38 years; Sands and earlier investigators were treating adolescents and young adults. (b) Diagnosis may bear some relation to therapeutic result. None of our four patients with congenital mental defect (including two mongoloids) showed any definite change; interestingly, one patient with senile psychosis had a good result.

An incidental observation of Sands' was confirmed in our study. In our series weight gain was associated with a reduction of sexual behaviour (two patients), and weight loss with absence of response (two patients). Absence of weight change may be associated with either response or absence of response to the drug.

Our study was not designed to attempt to find the optimal dose of stilboestrol for this use of the drug; rather we tried to obtain maximal response by using high doses. Dunn used a daily dose of 5 mg., while Sands obtained results with a weekly dose commencing at 1 to 2 mg., increased to a maintenance dose of 4 to 9 mg. weekly. Sands found that response was associated with a moderate degree of gynaecomastia, and regulated the dose accordingly. To judge from our data there is no increase in effectiveness with doses higher than 5 mg. daily, but a daily dose in the region of 2.5 to 5 mg. may produce more rapid effect than smaller doses. All authors who have used oestrogens in this type of study have noted reduction of libido within four to eight weeks.

No valid conclusions about the effect of stilboestrol on the EEG can be drawn from our results in two cases. We could find nothing in the literature pertinent to this question.

Recognized side-effects of stilboestrol—gynaecomastia, anorexia, nausea, vomiting, weight loss, and skin rashes—were observed inconstantly, as noted in the case reports. In no instance were the side-effects of sufficient severity to necessitate stopping the drug, although in two instances gastro-intestinal symptoms resulted in the daily dose being reduced to 1 mg. Other incidental complications which occurred are illustrative of the variety of problems that can arise during such a study. One patient had progressive carcinoma of the lip, one (No. 13) acquired what was probably a systemic viral infection, and one (No. 16), while on placebo, had epileptic seizures for the first time in his life, an effect which might have been attributed to the drug had he been on stilboestrol at the time.

Regarding theoretical aspects of this study, present evidence (1) indicates that testicular hormone is indispensable in the period of sexual maturation. The hormone promotes the functional maturation of the nervous centre subserving sexual behaviour, the anterior hypothalamus being of greatest importance. But later the neural apparatus acquires more or less autonomy, and psychic factors play a greater role in determining the degree of sexual activity. That sexual potency may exist in the absence of testicular hormone is a well-established fact; there are many reports of men castrated after puberty continuing to be sexually active.

Assuming, as seems justified (6), that oestrogen therapy produces in the male a chemical castration, we see in the present study the results of interplay between physical and psychic forces. For the group whose sexuality was suppressed by stilboestrol, psychic factors were apparently of secondary

importance, and sexual activity mediated the release of hormonally mediated sexual tension. Two of these patients showed a concomitant improvement in general behaviour, presumptive evidence that psychic conflict, stemming from a physiological sexual source, was temporarily eased by the suppression of sexuality. For the two patients who became worse on the drug, sexual activity, while evidently still partly dependent on testicular hormone, was used symbolically in resolving psychic conflict; when this means of expression was threatened, they became disturbed. For the patients who showed no significant change on the drug, sexuality was apparently largely independent of its hormonal substrate. Sexuality seems, in general terms, to have served them as a means of intensifying experience.

#### SUMMARY

Our experience at the Verdun Protestant Hospital with the use of stilboestrol in suppression of male sexual behaviour has been reviewed. This report deals chiefly with the results of administration of 1 to 10 mg. daily to fifteen patients in a controlled study. Six of the fifteen showed suppression of sexual behaviour, two became disturbed in relation to treatment with the drug, and the remainder manifested no definite change. The results are discussed in the light of present knowledge of the subject.

#### ACKNOWLEDGMENTS

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# EFFECTS OF 5-HYDROXYTRYPTOPHAN ON SCHIZOPHRENIA

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## INTRODUCTION

THE present investigation represents a logical continuation of a previous experiment where it was shown that the injection of 5-hydroxytryptophan (5HTP) alleviates the psychological effects of lysergic acid diethylamide (LSD-25) (Brenghelmann, Pare and Sandler, 1958). LSD is of interest in psychiatry because the psychotomimetic effects of the drug bear a resemblance to schizophrenia clinically, in psychological tests and, according to Hoagland, Rinkel and Hyde (1955), in their abnormal excretion of urinary phosphate. The possibility presents itself that, in some cases of schizophrenia, the functional abnormality is similar to that produced by LSD.

Gaddum (1953b) noted that LSD was an effective antagonist to the action of 5-hydroxytryptamine (5HT) on the peripheral tryptamine receptors of smooth muscle (Gaddum, 1953a). From this arose the concept that a central antagonism to 5HT might account for the psychological properties of LSD (Amin, Crawford and Gaddum, 1954). Evidence supporting this suggestion has recently been put forward by Brenghelmann, Pare and Sandler (1958). These authors showed that the psychological effects of LSD were reduced by increasing the brain concentrations of 5HT. This was done by giving the precursor substance 5HTP which, unlike 5HT, readily passes the blood brain barrier to be decarboxylated *in situ* to 5HT.

Woolley and Shaw (1954) suggested that schizophrenia may be caused by some naturally occurring LSD-like substance. If this is so, then the psychosis in these patients should also be relieved by 5HTP. This is the major hypothesis of the present investigation.

Any future work of a related kind may come up against the complication that only a certain type of patient benefits from a particular kind of treatment whereas others remain refractory. While the number of subjects used in the present investigation is obviously too small to study this point conclusively, a suggestive result may well provide a useful pointer for future research. For this

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reason, personality questionnaires of rigidity, extraversion and neuroticism were administered to the patients. It is known from previous (Bregelmann, 1958a, 1959), as well as from more recent unpublished results, that schizophrenia and questionnaire rigidity vary significantly in a similar manner when correlated with a number of objective test scores. The same experiments have, furthermore, shown that adaptation to external stimuli in terms of various learning and perceptual scores is lowest for schizophrenics and rigid subjects. From this, it may be inferred that if 5HTP does benefit schizophrenic patients, highly rigid schizophrenics will benefit less than those low in rigidity. No such relationship is expected for extraversion and neuroticism.

## METHOD

### 1. General Procedure

Eleven patients aged 18–65 years (mean 32 years) were selected because of the confidence in the diagnosis of schizophrenia, the acute phase of their illness and the fact that they were receiving no specific treatment. There were six male and five female subjects. Early morning specimens of urine were collected prior to the investigation proper from six of the eleven patients. Two-dimensional indole chromatograms and estimation of 5-hydroxyindoleacetic acid in mg./g. creatinine were done by methods described elsewhere (Bregelmann, Pare and Sandler, 1958).

Following a battery of psychological tests, the subject was given an intravenous injection of 25 mg. DL-5HTP in 5 ml. solution, or an equivalent amount of placebo. Two hours later the psychological tests were again administered. At the same time next day the investigation was repeated alternating the 5HTP and placebo.

### 2. Psychological Apparatus Tests

The psychological tests used have been described in a previous publication (Bregelmann, 1958b). The scores are briefly re-stated as follows.

*Perceptual Reaction Test (PRT): degree of variability.* In contrast to the previous single administration the PRT was now given three times on each occasion in order to increase reliability. The score was mean degree of variability, as before. This score was, however, computed as variability between the three administrations instead of between initial practice and subsequent occasions.

*After-image Duration:* duration of the negative after-image of a red square.

*Rotation Error (FRT):* error in reproducing the position of visually exposed stimuli (immediate recall).

*Positive or Subjective Recognition (FRT):* number of patterns "subjectively" recognized out of a total of 30, ten of which having been shown previously.

*Size Variability (FRT):* variability in the size of stimuli reproduced by drawing (expressive movement).

The first four scores are known to discriminate clearly between schizophrenics on the one hand and normals and neurotics on the other. Scores increased or decreased in the order: normals—neurotics—schizophrenics. The fifth score (size variability) discriminated as with the above pattern though not to a high degree. This score was mainly included because of the clear results it has yielded with regard to the effect of 5HTP on LSD effects (Bregelmann, Pare and Sandler, 1958).

### 3. *Personality Questionnaires*

The extraversion and neuroticism questionnaires used are those developed by Eysenck (1956). As a result of an item analysis, the rigidity questionnaire comprised the following items of a previously published scale (Bregelmann, 1959): 1, 3, 6, 7, 8, 9, 11, 13, 16, 17, 19, 20, 27 and 28. With 14 items, the range of scores is from 0 to 28, weights being 2 for each response in the rigid direction and 1 for an undecided response (question mark).

### 4. *Design and Predictions*

The order of tests was constant for all five occasions as follows: after-image, PRT I, rotation error I, subjective or positive recognition I, PRT II, rotation error II, subjective recognition II, PRT III. Testing lasted about one hour on each occasion. The following basic design was employed:

practice—control 1—post-injection 1—control 2—post-injection 2.

Placebo and 5HTP were assigned to injections 1 and 2 in a randomly balanced manner. The psychologist did not know which injection had been given.

If 5HTP acts to reduce schizophrenic effects towards normality, the following predictions must be made.

| <i>Predictions for Test Scores</i>    |    |    |    |    | <i>5HTP Score as Against<br/>Placebo or Control Conditions</i> |
|---------------------------------------|----|----|----|----|----------------------------------------------------------------|
| 1. PRT degree of variability          | .. | .. | .. | .. | lower                                                          |
| 2. After-image duration               | .. | .. | .. | .. | higher                                                         |
| 3. Rotation error                     | .. | .. | .. | .. | lower                                                          |
| 4. Positive or subjective recognition | .. | .. | .. | .. | lower                                                          |
| 5. Size variability                   | .. | .. | .. | .. | lower                                                          |

## RESULTS

### 1. *Objective Test Results*

Before discussing the results, a comparison is made between the present schizophrenic responses and the corresponding previous responses of normals (Bregelmann, 1958) in order to demonstrate the validity of the tests used in the present study. The schizophrenic scores deviated in the expected direction for all tests. With the exception of size variability, which has already been stated to be a relatively poor discriminator, the differences were considerable, as may be seen from a comparison between the present results (Fig. 1) and those obtained in the investigations already quoted.

The group means are shown in Figure 1. Some previous score norms are provided in dotted lines.

A comparison between the predictions made and Figure 1 reveals that the group trends of four of the five test scores (PRT, after-image, rotation error and recognition) contradict the expectation. Only size variability conforms with the prediction.

The directions of the individual responses are shown in Table I. Two comparisons are made over all 55 responses to the five tests. Firstly, 5HTP and placebo are compared with their own control tests. Secondly, 5HTP responses are assessed directly against placebo instead of its own control, thus using the placebo scores as a baseline. By this method, the number of events confirming or rejecting the hypothesis is then tested against the theoretically expected

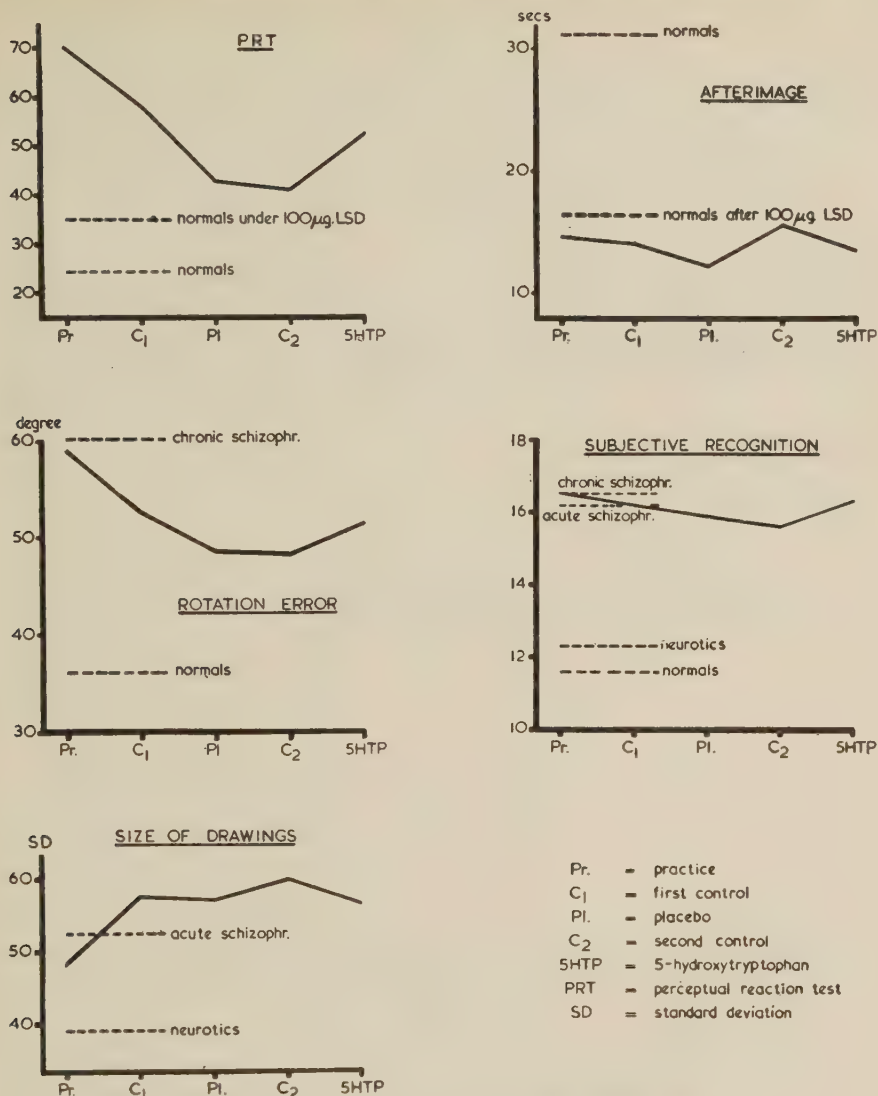


FIG. 1.—Group means of eleven acute schizophrenic patients.

frequency of 27.5 (half the total number of 55 responses). Most of the discussion is based on the latter comparison.

The first comparison shows that 25 of the 55 5HTP responses contradict the hypothesis. For placebo, 32 responses accord with the prediction made for 5HTP, suggesting that placebo was more beneficial than 5HTP. Testing the 5HTP results against placebo, a chi-square of 3.661 (1 d.f.) is obtained which is not significant at the 5 per cent. level.

As to the second comparison, 23 5HTP responses confirm the prediction, whereas 32 are contradictory. A test of these observed frequencies against the theoretically expected frequencies results in a chi-square of 1.472 (1 d.f.) which is not significant.



TABLE I

| <i>Direction of Individual Test Responses with Regard to Predictions</i> |    |   |   |   |   |                  |   |   |   |   |
|--------------------------------------------------------------------------|----|---|---|---|---|------------------|---|---|---|---|
| 5HTP vs. Own Control<br>(Placebo vs. Own Control)                        |    |   |   |   |   | 5HTP vs. Placebo |   |   |   |   |
| Tests                                                                    | 1  | 2 | 3 | 4 | 5 | 1                | 2 | 3 | 4 | 5 |
| 1                                                                        | .. | + | + | - | + | +                | - | - | + | - |
| 2                                                                        | .. | + | + | + | - | +                | - | - | - | - |
| 3                                                                        | .. | + | + | + | + | +                | + | + | + | - |
| 4                                                                        | .. | - | - | + | + | -                | - | - | - | + |
| 5                                                                        | .. | + | + | - | - | +                | + | - | - | - |
| 6                                                                        | .. | + | + | + | + | +                | - | + | + | + |
| 7                                                                        | .. | - | - | + | + | -                | + | - | + | - |
| 8                                                                        | .. | + | - | - | + | +                | - | - | - | - |
| 9                                                                        | .. | + | + | + | - | +                | + | - | - | - |
| 10                                                                       | .. | - | + | - | + | -                | - | - | + | - |
| 11                                                                       | .. | - | + | - | + | -                | + | - | + | + |

+ = score is reduced in normal direction.

- = score remains the same or is increased in the schizophrenic direction.

Values for 5-hydroxyindoleacetic acid (5HIAA) in early morning specimens of urine are expressed as mg./g. creatinine.

## 2. Questionnaire Results

Subject 7 refused to complete the questionnaires. Results obtained for all other subjects are shown in Table II.

TABLE II

### Questionnaire Scores of Rigidity, Extraversion and Neuroticism

| Subjects | Rigidity (R) |    |    | Extraversion (E) | Neuroticism (N) |
|----------|--------------|----|----|------------------|-----------------|
| 1        | ..           | .. | 26 | 10               | 8               |
| 2        | ..           | .. | 16 | 14               | 34              |
| 3        | ..           | .. | 14 | 19               | 27              |
| 4        | ..           | .. | 26 | 28               | 36              |
| 5        | ..           | .. | 18 | 15               | 22              |
| 6        | ..           | .. | 10 | 20               | 10              |
| 8        | ..           | .. | 8  | 27               | 20              |
| 9        | ..           | .. | 14 | 17               | 38              |
| 10       | ..           | .. | 20 | 32               | 17              |
| 11       | ..           | .. | 6  | 30               | 27              |

Dividing the ten subjects into the five most rigid and five least rigid patients, the following relationship to the effect of 5HTP on test performance (compare 5HTP/placebo section in Table I) is obtained (Table III).

TABLE III

*Rigidity Interacts Significantly with the Effect of 5HTP on Test Performance of Schizophrenics. "Prediction" Refers to the 5HTP/Placebo Comparison Shown in Table I*

|                       | Low R | High R | E  | I     | Low N | High N |
|-----------------------|-------|--------|----|-------|-------|--------|
| For prediction        | ..    | 14     | 7  | 10    | 11    | 10     |
| Against prediction    | ..    | 11     | 18 | 15    | 14    | 15     |
| Chi-square            | ..    | 4.024  |    | 0.082 |       | 0.082  |
| Significance (1 d.f.) | ..    | 5%     |    | N.S.  |       | N.S.   |

Of the 25 predictions pertaining to the five most rigid subjects, 18 are found to vary against and 7 in favour of the main hypothesis, that 5HTP reduces test responses towards normality. The corresponding figures for the low rigidity sub-group are 14 for and 11 against the hypothesis. This relationship is significant at the 5 per cent. level (2.5 per cent. for a one-tail test) as expressed by a chi-square test of independence. The corresponding relationships for extraversion and neuroticism are clearly insignificant. This result confirms the prediction that rigidity interacts significantly with the effects of 5HTP on the test performance of schizophrenics.

### 3. *Sex*

Patients 1, 4, 5, 9 and 10 were of female, the rest of male sex. An inspection of Table I (5HTP/placebo portion) shows that of the 25 predictions for the five female patients eight were for and seventeen against the prediction. The corresponding figures for the six males were each fifteen for and against. This relationship is not significant ( $\chi^2 + 1.809$ , 1 d.f.).

### 4. *Biochemical Results*

Using patients numbered 4, 5, 6, 8, 9 and 11, an attempt was made to correlate the effect of 5HTP on the psychological test scores on the one hand, with the urinary excretion of 5HIAA and the pattern of the urinary indole chromatogram on the other (Table I). No systematic relationship was found between the biochemical and psychological findings.

### 5. *Conclusions*

The hypothesis that 5HTP will alter the psychological scores of schizophrenics as an unselected group in the direction of normality has not been confirmed. The results obtained contradict the hypothesis but not significantly so. The suggestion is made that this effect of 5HTP on performance may be significantly dependent on the personality trait of rigidity as defined by the questionnaire method.

## DISCUSSION

The results of the present investigation must be interpreted in the light of the authors' previous paper, where a marked alleviation of some psychological effects of LSD in normals by 5HTP was found. In the present investigation on schizophrenia, where the investigators, the environment and the experimental method were similar, the overall results showed, if anything, a slight worsening of the psychological abnormalities. This is in conformity with the experience of Hoagland (1958) who gave daily doses of 100 mg. 5HTP to schizophrenics for two weeks without noticing any improvement in their mental state.

The significant interaction obtained between personality rigidity and the effect of 5HTP on test performance may be of importance though apparently not with regard to the expected benefit of 5HTP injection. As Table III indicates, the main contribution to the significance of the result is on the negative side of the prediction. In other words, it may be suggested that the combination of high rigidity and 5HTP injection leads to a deterioration of performance whereas low rigid patients are little effected by the injection. This formulation does not consider the beneficial effect of 5HTP but simply relates to unspecific drug effects.

Leyton (1958) has suggested that a group of schizophrenics may be identified by their low urinary excretion of 5HIAA and that this group of patients benefits from the injection of 5HTP. In six subjects so tested there was no suggestion that patients with a low urinary excretion of 5HIAA responded to 5HTP any better than those with a higher rate of excretion. Though the number of patients is too small to warrant any suggestion, it should be noted that the results did not support Leyton's hypothesis.

Finally, it may be stated that the suggestion made by Woolley and Shaw (1954) that schizophrenia may be caused by some naturally occurring LSD-like substance has not been confirmed.

## SUMMARY

The hypothesis was tested that excess of brain 5-hydroxytryptamine (5HT), as produced by the injection of 5-hydroxytryptophan (5HTP), leads to a reduction of psychotic test effects in schizophrenics. The perceptual and memory tests used had previously been validated on abnormals and in LSD research with normals. The hypothesis was not confirmed.

## ACKNOWLEDGMENTS

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# STUDIES IN SCHIZOPHRENIA—VI

## PAPER CHROMATOGRAPHY OF URINARY INDOLES AND THE "GLYOXYLIC ACID" REACTION

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THE following is a short report on the results obtained from 204 two-way paper chromatograms for urinary indoles. The material examined came from 58 schizophrenics, 34 organic psychoses, 58 affective psychoses (33 complicated by physical disease, and 25 not), 48 neurotics etc. (18 complicated by physical disease and 30 not) and 6 mentally normals.

The urines were with few exceptions, first morning specimens from new admissions, sent to the laboratory for routine examinations. They came from 98 men and 100 women from three and two admission wards respectively, and 6 female staff. The specific gravity was on the average 1.020, with average variations of  $\pm 0.008$ .

The tests carried out for the purpose of this examination were:

1. *Two-way paper chromatography*: 2 ml. of clear urine contained in a 10 ml. beaker were concentrated *in vacuo* over phosphoric oxide. In this way a four- or five-fold reduction in volume could be obtained within 24 hours. The volume was measured and the equivalent of about 100  $\mu$ l of the original specimen submitted to ascending two-dimensional chromatography using the solvent system of Jepson (7). If the concentrate could not be used at once it was stored overnight at 4° C. in a 5 ml. screw-capped bottle. The concentrate was spotted 3 cm. from the lower right-hand corner of 10 inches square Whatman No. 4 filter paper using a platinum loop constructed to hold 5  $\mu$ l. of water. Each spot was dried in a stream of warm air (about 45° C.) before a further drop of concentrate was added. Loaded papers were first run in isopropanol-water-ammonia (200–20–10) (IPRAM) overnight (16 hours), the lid of the tank being sealed with 50 per cent. glycerol solution. After thorough drying in a stream of unheated air, the second run was made at right-angles to the first in n-butanol-water-acetic acid (120–50–30) (BuA) for six hours. After drying in an unheated air-stream the papers were drawn through Ehrlich reagent (Jepson (7)) contained in a shallow trough (10 ml. of a 10 per cent. solution of p-dimethylaminobenzaldehyde in pure HCl diluted to 50 ml. with redistilled acetone). The papers were observed continuously for the first 5–10 minutes, periodically for the next hour and finally examined the following morning. Spots were ringed with soft pencil as they appeared. Notes were made of colours, their intensity and speed of development and of any colour changes as they became established.

2. The "glyoxylic acid" ("g.a.") reaction (as described by Fleischhacker and Lancaster (5)), followed by chloroform (or carbon tetrachloride) extraction. The glyoxylic acid reagent was used throughout and specific gravities were not adjusted.

3. The Obermeyer test for indican. Attention was paid to the question of treatment of patients. Diagnoses were obtained only after all laboratory tests had been completed, and as a rule several weeks after admission in order to give the clinician time to make his diagnosis. The schizophrenic group consisted of idiopathic and also a number of "symptomatic" schizophrenics; the "organic" group consisted mainly of patients suffering from arteriosclerotic and senile dementias and also a few with Huntington's Chorea and epileptic and other psychoses. The complications of the affective and neurotic group (the latter containing also some patients with psychopathic personality) were mainly vascular and heart disease, metabolic disorders, alcoholism and peptic ulcers.

## RESULTS

### 1. Chromatography

The number of spots excluding urea, varied between two and fourteen per person in the following way:

|                   |    |     |     |      |              |
|-------------------|----|-----|-----|------|--------------|
| Number of spots   | .. | 2-4 | 5-7 | 8-10 | More than 10 |
| Number of persons | .. | 54  | 97  | 46   | 7            |

On the whole there was no essential difference in the number of spots per person in connection with sex or age, and, as far as could be ascertained, the administration of drugs (e.g. sodium amytal, and, in a few cases Largactil), nor is there any clear relation to the concentration of indican as demonstrated by the Obermeyer reaction. Other workers too (Rodnight and Aves (11), Curzon (3)) have not found the connection in this respect as claimed by Sano (12). It is true that when the Obermeyer reaction was weakly positive, only 2 to 4 spots were more frequently found; but often with a very outspoken Obermeyer reaction the number of spots was also small. The number of spots was often somewhat larger in urines of high specific gravity and somewhat smaller when the specific gravity was low; but again this was not invariable.

In the different groups the average number of spots per person were as follows:

|                       |    |    |     |                         |    |    |     |
|-----------------------|----|----|-----|-------------------------|----|----|-----|
| Schizophrenic         | .. | .. | 6.3 | Organic psychoses       | .. | .. | 6.2 |
| Complicated affective | .. | .. | 6.3 | Uncomplicated affective | .. | .. | 6.1 |
| Complicated neuroses  | .. | .. | 6.1 | Uncomplicated neuroses  | .. | .. | 5.5 |
| Mentally normal       | .. | .. | 6.0 |                         |    |    |     |

Patients with more than 8 spots were somewhat more frequent in the schizophrenic, complicated affective and complicated neurotic than in the other groups.

Altogether over 30 different spots were seen, a number of them very faint and soon disappearing, others more intense and lasting for several hours or even longer. The colours seen were yellow, brown, pink, purple, blue, grey, green and intermediate shades. Excluding those of the yellow, yellow-brown, brown series, there were 26 different spots seen, some very rarely. Of these, 13 appeared in more than 10 per cent. and have positions which agree quite well with those on the chart published by Buscaino and Stefanachi (1); but only 7 spots appeared in 40 per cent. or more of the material (including indoxyl

sulphate, present in all). It is with these 7 spots that we are dealing in this communication.

It may be mentioned in brief that of the rarer spots none apparently were characteristic of any groups, except possibly spot 12 (see later).

Slight variations in technique (temperature, filter paper, and so on) can introduce variations in the position and intensity of spots, as can be seen from charts published by different authors, and this has to be borne in mind when considering the following map. The spots are numbered in order of frequency with which they were found in our material.

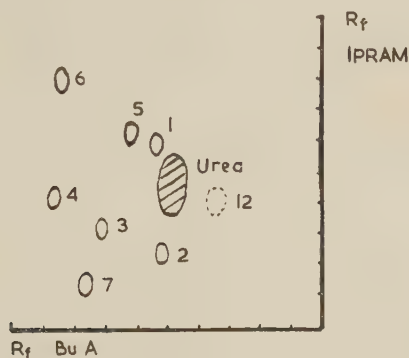


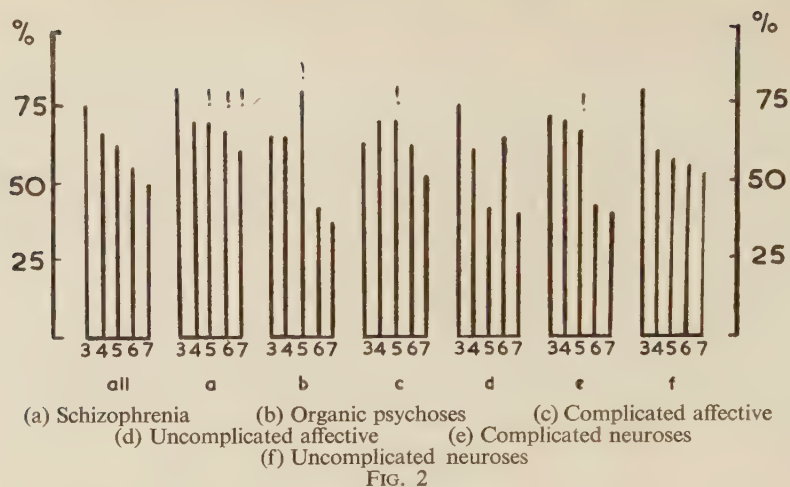
FIG. 1

1. Indoxyl sulphate.
2. Tryptophan.
3. Probably indolyacetyl glutamine.
4. Probably 3-indolyacetic acid.
5. A not definitely defined substance, possibly a skatol derivative (Buscaino and Stefanachi's 3, Leyton's S, Riegelhaupt's Q.F.B. (although it often did not fade very quickly in our material), Rodnight's U.2).
6. Position similar to that of tryptamine, but it is probably not this substance (Rodnight and Aves (11)).
7. Probably 5-hydroxy-indolyl acetic acid.
12. Slightly bluish-green, Rf 42/35, appearing late (after 20-45 minutes) and still visible after 18 hours (? Buscaino and Stefanachi's 8 (1) and Riegelhaupt's 54/33 (10)). Present in about 15 per cent. of schizophrenic, organic and complicated psychoses, mainly in urines yielding at least 6 spots, independent of high-intensity spots, sex and age.

The following histogram illustrates the distribution of spots 3 to 7 in the different groups. Spots (1) which appeared in all, and (2) which appeared in 88 per cent. to 96 per cent. of all groups are omitted. In each group all these spots appeared in at least 40 per cent. of urines examined.

We have marked by ! those spots where frequency of appearance may have some characteristic meaning particularly in combination with the others in this or that group, e.g. spot 5 is a little more frequent in schizophrenics and other "organic" conditions; spot 12 did not appear in any of the uncomplicated neurotics, but it was present only in 15 per cent. of the other groups. If spot 4 is omitted, the number of the more common spots is highest in schizophrenics, which agrees with Rodnight and Aves' findings. On the other hand, it was not possible to find any obvious difference between idiopathic and symptomatic schizophrenia or arteriosclerotic and senile dementia.





It is clear from this that none of these substances as such can be of any diagnostic significance and the purely qualitative aspect of indole-compound chromatography in urines will not lead us any further. Papers published by other authors (Sano (13), Curzon (3) and Leyton (8)) confirm this view. On the other hand there are some differences which need not necessarily be due to external circumstances. They may be an indication of metabolic variations in different individuals, either as a consequence of disturbed functions, or as predisposing them. It can also not be excluded that differences in pattern are not only of a qualitative but also of a quantitative nature.

We found great difficulty in evaluating the intensity of spots except where variation from "average" was extreme. Although quite a number of faint or very faint spots were seen, only 33 from 24 people were thought to be of striking intensity, amongst them, most often, spot 6. They were all found in chromatograms with at least 6 spots and in all 6 groups to the same extent. The results of authors who have attempted semi-quantitative estimations (Curzon, Rodnight and Aves, Leyton, Sano (13) and Buscaino and Stefanachi (2)) show several contradictions as can be seen from their papers. If one considers the mere frequency of spots in the different groups, there are marked variations between Rodnight and Aves and ourselves with regard to indolylacetyl glutamine and 5-hydroxyindolacetic acid which we found somewhat more often, and 3-indolylacetic acid which was more frequent in their material.

From all this it appears that much more rigid metabolic and chromatographic techniques have to be used, if conclusive information is desired.

## 2. The "Glyoxylic Acid" ("g.a.") Reaction

In order to demonstrate dysmetabolism of tryptophan in schizophrenics Riegelhaupt (9) applied the "g.a." reaction to urines. He found it positive in many cases and took this, like other authors later on (Curzon, Leyton and to a certain degree also the present authors (4, 5, 6)), as a confirmation of this hypothesis. Subsequently, we have shown that it was positive not only in idiopathic schizophrenic, but also in many other organic psychoses and even some mentally normal people when they were acutely physically ill (Fleischhacker and Lancaster). It was also observed in a few cases of acute mental disorders that the reaction was negative when it was expected to be

positive (Fleischhacker, Lancaster and Wheeler). In this investigation the results in the different groups were as described previously (Fleischhacker and Lancaster), but the number of positive and doubtful tests was smaller than expected in this more acute material, thus confirming our former experience (Fleischhacker, Lancaster and Wheeler).

Riegelhaupt (9) had tentatively concluded that there is no connection between the outcome of the "g.a." test and indican excretion, and we have shown that this is correct in principle (Fleischhacker and Lancaster). Curzon thought that an increase of tryptophan in urine may contribute to a positive "g.a." reaction, but we thought this to be unlikely and had considered that catalysts may be at play (Fleischhacker and Lancaster). Riegelhaupt (10) working in another laboratory and using the urines of a small number of selected Shenley patients thought that there might be a relation between a positive reaction and his spot Q.F.B. (probably our spot 5). This spot, however, occurs rather frequently in other conditions too. It has also been found in many mentally normal people by other workers, who took it as a product of hospitalization, a view not confirmed by us, or by Rodnight and Aves, in acute mental patients and some normals.

The reading of the "g.a." test was made particularly critically and many results were classified as doubtful (with four exceptions, all in the groups of schizophrenic, organic and "complicated" affective or "complicated" neurotic illnesses). No connection was found between the positive or negative result of the "g.a." test and any spot, combination of spots, or their intensity. In some cases the reaction was positive in the presence of indoxyl sulphate and tryptophan only; yet we know that in ordinary circumstances it is most unlikely that these substances give rise to a positive "g.a." reaction in urine, apart from the fact that on other urines where chromatograms gave only these 2 spots, it was negative. If one goes by the qualitative chromatographic pattern of indole-compounds as described here, there is either no relationship at all, or an extremely complicated one between this and the "g.a." reaction.

#### SUMMARY

1. The present paper chromatographic investigation for indole compounds in the urine of schizophrenics, and "organic" and "non-organic" control groups shows that qualitative differences in the excretory pattern between the various groups are of no definite diagnostic or pathogenetic value. This agrees with the work of some other authors. Fully quantitative examinations of the individual compounds under strictly controlled metabolic conditions will be more valuable; the present investigation does not make any contribution in this respect.

2. No connection was found between positive or negative "glyoxylic acid" reactions and any spot, combination of spots, or their intensity.

3. Previous impressions on the diagnostic significance of the "glyoxylic acid" reaction have been confirmed in principle, though it is possibly less often positive in acute mental patients than formerly thought.

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# THE RELATIVE STABILITY OF PERSONALITY MEASURES COMPARED WITH DIAGNOSTIC MEASURES

By

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## INTRODUCTION

IN previous investigations (Foulds and Caine, 1958 and 1959) psychoneurotic subjects were classified in terms of the presenting syndrome (Hysteria or Dysthymia) and of the personality type (hysteroid or obsessive) as rated by psychiatrists. It was found that some psychological test measurements differentiated between Hysterics and Dysthymics regardless of personality type; whilst other measures differentiated between hysteroid and obsessive personalities regardless of diagnosis. The successful measures were not, however, identical for men and women. It was argued that one of the advantages of this double classificatory system should be that we would have one set of measures—the diagnostic—which should vary with the patient's clinical condition and another set—the personality measures—which should remain relatively constant.

The aims of the present investigation were two-fold: firstly, to repeat the study of symptom clusters and personality trait clusters with a new sample of psychoneurotic women; secondly, in the event of confirmatory findings, to test the prediction that personality measures would prove more invariable than diagnostic measures. Following from this and from the fact that Dysthymic women were more often considered to recover from their illness than Hysterics (Foulds and Caine, 1959), a subsidiary pair of predictions can be made. The first is that on re-test the diagnostic measures of the Dysthymics will change more than those of the Hysterics; the second is that hysteroid and obsessive patients will change equally little on the personality measures. Thus, Hysterics and Dysthymics should differ significantly on the diagnostic measures on first testing; but they should be indistinguishable on second testing after an interval of, say, one month. Hysteroid and obsessive subjects should, however, be significantly different on the personality measures at both first and second testing.

## REPLICATION STUDY

*Subjects and their classification:* Twenty-three successive admissions, diagnosed as psychoneurotic, were tested. To these were added 3 of the 4 Hysterics of obsessive personality who were not used in the earlier study. The fourth has subsequently been thought to be a Paranoid Schizophrenic. The final groupings were as follows: 8 hysteroid Hysterics (Hh); 5 obsessive Hysterics (Ho); 7 hysteroid Dysthymics (Dh) and 6 obsessive Dysthymics (Do.).

The 13 Hysterics had a mean age of 37.69 years (s.d. 10.73) and the 13 Dysthymics 36.46 (s.d. 9.56). The difference was not significant.

The 15 hysteroid patients had a mean age of 35.00 years (s.d. 8.72) and

the 11 obsessive 39·91 (s.d. 11·27). Again the difference did not approach the 5 per cent. level of significance.

*The tests:* These were, of course, identical with those used in the earlier study—the Mill Hill Vocabulary Scale, the Progressive Matrices (1938), the Porteus Mazes, the Thematic Apperception Test, the Minnesota Multiphasic Personality Inventory, the Superiority-Inferiority Index and the Tapping Test.

The sole difference in administration was that Progressive Matrices was given without a time limit and without, rather than with, the patient being aware that the time taken was being recorded.

*Scoring:* In the earlier study the scores on each test were cut into quintile divisions. Those falling within the first quintile score  $-2$  (the Dysthymic end in the case of the diagnostic measures, the obsessive end in the case of the personality measures) and so through to  $+2$  at the Hysteric or hysteroid end. Subjects in the present study were scored in accordance with these tables based on the original sample.

*Results:* Table I shows the number of cases correctly identified. The percentages correctly identified in the original study were both 78; in this study they were both 77. The previous findings have, therefore, been confirmed.

TABLE I

*Number and Percentage of Cases Correctly Identified as to Diagnostic and Personality Type*

|                                | 8 Hh | 5 Ho | 7 Dh | 6 Do | 26 Total | Per cent. |
|--------------------------------|------|------|------|------|----------|-----------|
| Correct as to diagnostic type  | 6    | 3    | 6    | 5    | 20       | 77        |
| Correct as to personality type | 6    | 5    | 5    | 4    | 20       | 77        |

The numbers are too small to allow convincing cross-validation of each test. All of them, however, apart from the Tapping Test, classified correctly more subjects than they misclassified, the percentages ranging from 55 to 78. The earlier promise of the Tapping Test—based on less than the original total sample—was not fulfilled. The sixth personality measure—M.M.P.I.: Hy+Pd+Sc+Pt—was abandoned as cumbersome and adding nothing significant to the overall differentiation.

The change in administration of Progressive Matrices resulted in the reappearance of the Matrices : Vocabulary ratio differences (Foulds, 1956). The mean Mill Hill Vocabulary grade for the 13 Hysterics was 5·15 and the mean for Progressive Matrices 5·00; the corresponding figures for the 13 Dysthymics were 5·38 and 4·38. Whilst letting the patient know that she was being timed on the Matrices made no significant difference in the speed of work, it did apparently cause the Dysthymics to make more errors.

Tentative norms based on the 64 cases in the original study and the 26 cases in the present study are given in the Appendix. Quintile divisions are replaced by septile divisions.

#### RE-TEST STUDY

*Subjects and their classification:* Of the 23 successive admissions used in the replication study 19 were re-tested. The remaining 4 discharged themselves within 2 weeks of first testing. All 7 cases from the original study who had been re-tested were added. The final grouping was as follows: 8 Hh; 4 Ho; 6 Dh and 8 Do.

*Results:* To test the first prediction—that the diagnostic measures would change, without specifying direction, more than the personality measures—the difference between each subject's first and second test performance on each test regardless of direction was calculated. The mean difference for the three diagnostic and five personality measures was then obtained for each subject and the latter subtracted from the former. The mean difference for the group was then calculated and the t-test for the significance of a single mean applied. Thus, to give a typical example, if a subject's score on "Maze Distraction" fell in the first quintile on first testing she would score  $-2$ ; if, on second testing her score fell in the fourth quintile, she would score  $+1$ . The difference would then be 3. A complete example would be as follows:

|                 |    |    |         |          |           |   | Diagnostic |
|-----------------|----|----|---------|----------|-----------|---|------------|
|                 |    |    |         |          |           |   | Score      |
| 1st test        | .. | .. | Mz dis. | TAT:T.W. | MMPI D-Hs | = |            |
| 1st test        | .. | .. | $-2$    | $-1$     | $-1$      | = | $-4$       |
| 2nd test        | .. | .. | $1$     | $0$      | $1$       | = | $2$        |
| Difference      | .. | .. | $3$     | $1$      | $2$       | = | $6$        |
| Mean difference | .. | .. |         |          |           | = | $2.00$     |

|                 |    |     |         |         |          |     | Person-  |
|-----------------|----|-----|---------|---------|----------|-----|----------|
|                 |    |     |         |         |          |     | ality    |
|                 |    |     |         |         |          |     | Score    |
| 1st test        | .. | 1   | Mz T.T. | Mz L.P. | MMPI Ex. | S-I | P.M.T.   |
| 1st test        | .. | $1$ | $0$     | $-1$    | $2$      | $1$ | = $3$    |
| 2nd test        | .. | $2$ | $0$     | $0$     | $2$      | $2$ | = $6$    |
| Difference      | .. | $1$ | $0$     | $1$     | $0$      | $1$ | = $3$    |
| Mean difference |    |     |         |         |          |     | = $0.60$ |

The mean difference personality score of  $0.60$  is then subtracted from the mean difference diagnostic score of  $2.00$  for a final figure of  $+1.40$ . This might

be expressed as  $\frac{d_1-d_2}{3} - \frac{p_1-p_2}{5}$  where  $d$  is the diagnostic,  $p$  the personality

measure, where 1 and 2 refer to 1st and 2nd testing and 3 and 5 to the number of tests making up the diagnostic and personality scores respectively. The mean difference score for the group was  $0.652$  (s.d.  $1.137$ ),  $t=2.92$  and  $p$  is  $<.01$ . The first prediction that diagnostic measures would change more than would personality measures was, therefore, confirmed.

To test the second prediction mean diagnostic and personality scores were calculated for both groups on 1st and 2nd testing. These are shown in Table II, together with the  $t$  and  $p$  values.

TABLE II  
*Diagnostic and Personality Scores of Psychoneurotic Women*

|               |    | Diagnostic Scores |      |               |      | Personality Scores |      |               |      |
|---------------|----|-------------------|------|---------------|------|--------------------|------|---------------|------|
|               |    | 1st ( $d_1$ )     |      | 2nd ( $d_2$ ) |      | 1st ( $p_1$ )      |      | 2nd ( $p_2$ ) |      |
|               |    | Mean              | s.d. | Mean          | s.d. | Mean               | s.d. | Mean          | s.d. |
| 12 Hysterics  | .. | 3.08              | 3.73 | 2.25          | 2.56 |                    |      |               |      |
| 14 Dysthymics | .. | $-1.29$           | 3.99 | 2.00          | 2.88 |                    |      |               |      |
| 14 Hysteroids | .. |                   |      |               |      | 3.21               | 5.00 | 5.21          | 4.61 |
| 12 Obsessives | .. |                   |      |               |      | $-3.58$            | 4.59 | 0.67          | 5.21 |
| t             | .. | 3.04              |      | 0.22          |      | 3.57               |      | 2.26          |      |
| p             | .. | $<.01$            |      | $>.20$        |      | $<.01$             |      | $<.05$        |      |



Hysterics differed from Dysthymics on the diagnostic score at the 1 per cent. level of significance; after 4.69 weeks (s.d. 1.98) they did not differ at all.

Hysteroid patients differed from obsessives on the personality score at the 1 per cent. level of significance; on re-testing they still differed, but only at the 5 per cent. level of significance. The second prediction was, therefore, confirmed. There was, however, a tendency for obsessives to change rather more than hysteroids. This was particularly so on the two speed measures, Maze total time and Matrices time. Practice effect, which would work against the predictions, was not allowed for, except in considering the percentage of cases correctly identified. Here the optimal cutting score lay between 2 and 3 for personality re-test score instead of between 0 and -1 as on the first test.

On the first diagnostic score 77 per cent. were correctly identified (75 per cent. of Hysterics and 79 per cent. of Dysthymics); on re-test only 54 per cent. were correctly identified (83 per cent. of Hysterics and 29 per cent. of Dysthymics). Within the present framework, Dysthymics have moved towards the Hysteroid position. There is, however, some evidence that Hysterics behave more like normals than do Dysthymics—for example, in frequency of eye-blinks during conditioning (Franks, 1956a, b, 1957); on the E and N scales of the Maudsley Personality Inventory (Sigal *et al.*, 1958) and on the Mill Hill Vocabulary: Progressive Matrices ratio (Foulds, 1956). This movement of the Dysthymics may, therefore, be towards normality. This is lent some support by the fact that the M.M.P.I.: Depression scores of Dysthymics drop significantly, as can be seen from Table III.

TABLE III

*M.M.P.I.: Depression and Hypochondriasis Scales for Test-Re-test*

|         | 12 Hysterics |       |                      |       | 14 Dysthymics |       |                      |       |
|---------|--------------|-------|----------------------|-------|---------------|-------|----------------------|-------|
|         | Depression   |       | Hypo-<br>chondriasis |       | Depression    |       | Hypo-<br>chondriasis |       |
|         | Mean         | s.d.  | Mean                 | s.d.  | Mean          | s.d.  | Mean                 | s.d.  |
| Test .. | 71.50        | 17.83 | 71.33                | 18.72 | 79.07         | 14.89 | 64.71                | 10.19 |
| Re-test | 68.17        | 19.71 | 67.08                | 16.53 | 68.64         | 10.70 | 59.43                | 11.11 |
| t ..    |              |       |                      |       | 2.58          |       |                      |       |
| p ..    |              |       |                      |       | <.05          |       |                      |       |

On the first personality score 81 per cent. were correctly identified (78 per cent. of hysteroids and 83 per cent. of obsessives); on re-test 69 per cent. were correctly identified (79 per cent. of hysteroids and 58 per cent. of obsessives).

#### SUMMARY

Previous results—indicating that certain test measures differentiated between Hysteroid and Dysthymic women regardless of personality type, whilst others differentiated between hysteroid and obsessive personalities regardless of diagnostic type—were confirmed on a second sample.

It was predicted that (i) diagnostic measures would change more than personality measures; (ii) the diagnostic measures of Dysthymics would change more than those of Hysterics in such a way that (a) these groups would cease to be distinguishable on re-test; whereas (b) hysteroid and obsessive personalities would be distinguishable both on test and re-test. All these predictions were correct.

Those therapists who are, probably quite rightly, dissatisfied with the mere alleviation of symptoms may care to try to change some of the personality scores utilized here.

#### ACKNOWLEDGMENTS

I would like to thank Dr. R. Ström-Olsen, Physician Superintendent, for permission to publish this report and Dr. G. Fraser Steele and the psychiatric staff of his Division for carrying out the rating procedure.

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## APPENDIX

Mann Whitney U for  $n_2 > 20$  (2 tailed) for tests making up the diagnostic and personality scores

|                            | Hh<br>z | Dh<br>p | Hh<br>z | Do<br>p | Dh<br>z | Do<br>p |
|----------------------------|---------|---------|---------|---------|---------|---------|
| Maze distraction .. ..     | 2.27    | .023    | 2.23    | .026    | 0.10    | .920    |
| T.A.T.: Total Words ..     | 2.54    | .011    | 1.38    | .168    | 1.22    | .222    |
| M.M.P.I.: D-Hs .. ..       | 2.41    | .016    | 2.34    | .019    | 0.63    | .529    |
| Maze time .. ..            | 0.65    | .516    | 2.14    | .032    | 2.29    | .022    |
| Maze lifted pencils ..     | 0.23    | .818    | 2.72    | .007    | 2.64    | .008    |
| M.M.P.I.: Extrapunitive .. | 0.52    | .603    | 2.01    | .044    | 1.60    | .110    |
| Superiority-Inferiority .. | 0.66    | .509    | 3.05    | .002    | 1.86    | .063    |
| Matrices time .. ..        | 0.70    | .484    | 2.80    | .005    | 3.60    | .0003   |

## "Diagnostic" Tests

| Maze Distraction | TAT: Total Words | M.M.P.I.: D-Hs  |
|------------------|------------------|-----------------|
| +3 85 and over   | +3 115 and over  | +3 -4 and under |
| +2 77 to 84      | +2 106 to 114    | +2 -3 to +2     |
| +1 71 to 76      | +1 95 to 105     | +1 3 to 6       |
| 0 68 to 70       | 0 83 to 94       | 0 7 to 12       |
| -1 60 to 67      | -1 72 to 82      | -1 13 to 16     |
| -2 51 to 59      | -2 60 to 71      | -2 17 to 21     |
| -3 50 and under  | -3 59 and under  | -3 22 and over  |

## "Personality" Scores

| Maze Time        | Maze<br>Lifted Pencils | M.M.P.I.<br>Extrapunitive | Superiority-<br>Inferiority | Matrices Time   |
|------------------|------------------------|---------------------------|-----------------------------|-----------------|
| +3 209 and under | +3 2 and under         | +3 13 and over            | +3 7 and over               | +3 23 and under |
| +2 210 to 249    | +2 3 to 5              | +2 10 to 12               | +2 5 to 6                   | +2 24 to 30     |
| +1 250 to 296    | +1 6 to 8              | +1 8 to 9                 | +1 2 to 4                   | +1 31 to 37     |
| 0 297 to 339     | 0 9 to 11              | 0 6 to 7                  | 0 1                         | 0 38 to 50      |
| -1 340 to 379    | -1 12 to 14            | -1 5                      | -1 0                        | -1 51 to 65     |
| -2 380 to 499    | -2 15 to 19            | -2 3 to 4                 | -2 -1 to -2                 | -2 66 to 86     |
| -3 500 and over  | -3 20 and over         | -3 2 and under            | -3 -3 and under             | -3 87 and over  |

# OBSERVATIONS ON AROUSAL FOLLOWING MEGIMIDE (BEMEGRIDE) DURING LIGHT BARBITURATE NARCOSIS

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IN 1954 Shaw *et al.* described the action of Megimide (bemegride) in shortening sleep and restoring consciousness in laboratory animals under the influence of barbiturates. Subsequently, in 1955 Shulman *et al.* reported the results of the use of this drug in the treatment of barbiturate overdosage in man. Since then Megimide has been widely accepted as a valuable antidote in barbiturate poisoning, but there has been much discussion on whether it is a specific antagonist to barbiturates or a non-specific central analeptic.

Cass (1956) working with rabbits found that Megimide produced minimal E.E.G. changes in animals depressed by non-barbiturate hypnotics and concluded that the more pronounced reversal of activity produced by Megimide after barbiturates "may indicate a more specific pharmacological antagonism towards them". Other workers (Dotevall and Herner, 1957, Rowell, 1957, Söderberg, 1958) have, however, since claimed that following a variety of different anaesthetics Megimide has a restorative action similar to that after barbiturates.

Louw and Sonne (1956) and Pederson (1956) demonstrated that Megimide does not influence the rate of barbiturate elimination or the blood barbiturate level on awakening or the actual duration of coma. Their results gave no support to the hypothesis of a biochemical antagonism between Megimide and barbiturates.

Megimide has been considered to be a central stimulant on account of discharges observed in the E.E.G. when the drug was administered to subjects not under the influence of barbiturates. Furthermore similar E.E.G. changes have been observed after the administration of very large doses of Megimide in cases of severe barbiturate poisoning. Peacock (1956), however, could find no specific pattern of E.E.G. changes attributable to Megimide administration. Thomson (1958) studied volunteers given Megimide after sleep had been induced by oral barbiturate and found that the E.E.G. records gave no indication when awakening was about to occur, there being no significant E.E.G. change until the subject moved and awoke.

Most of the E.E.G. studies reported in man have been concerned with severe barbiturate intoxication, barbiturate anaesthesia or deep sleep induced by

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barbiturates. Under these conditions it is not always possible to study clearly the effect of Megimide administration on the 15-30 c/sec. activity which is considered to be a specific effect of barbiturates. If Megimide has a specific antagonistic effect towards barbiturates a reduction in these frequencies might be expected as a result of its administration.

In the present investigation E.E.G. records were taken from volunteer subjects in whom a light barbiturate narcosis was very slowly induced making possible a particular study of the barbiturate fast activity. In order to study central stimulating effects, finger plethysmographic records were taken from each subject as previous work (Ackner and Pampiglione 1957) had shown that the cutaneous vasoconstrictor response commonly followed E.E.G. changes evoked by stimuli during sleep. Continuous recordings of pulse rate and respiratory changes were also available.

In 50 psychiatric patients a light barbiturate narcosis was induced by the intravenous injection of sodium amytal at a rate of 0.5 mg./Kg. body-weight every 40 seconds until the subject failed on two consecutive occasions to give a verbal response. After an interval of about 3 minutes Megimide (50 mg. in 0.5 per cent. solution) was injected and this was repeated at 3-minute intervals until a verbal response was again obtained.

In the majority of cases the E.E.G. changes were those of light sleep and only in a few was there any marked slow wave activity. The onset of sleep was in most cases shortly preceded by a vasodilatation which reached its maximum by the time the sleep was fully established.

The injection of Megimide did not cause any characteristic pattern of change in the E.E.G., plethysmographic, respiration or pulse rate records (Fig. 1). Spontaneous awakening was uncommon and when arousal occurred it usually followed a verbal stimulus. Awakening was fairly sudden, even though

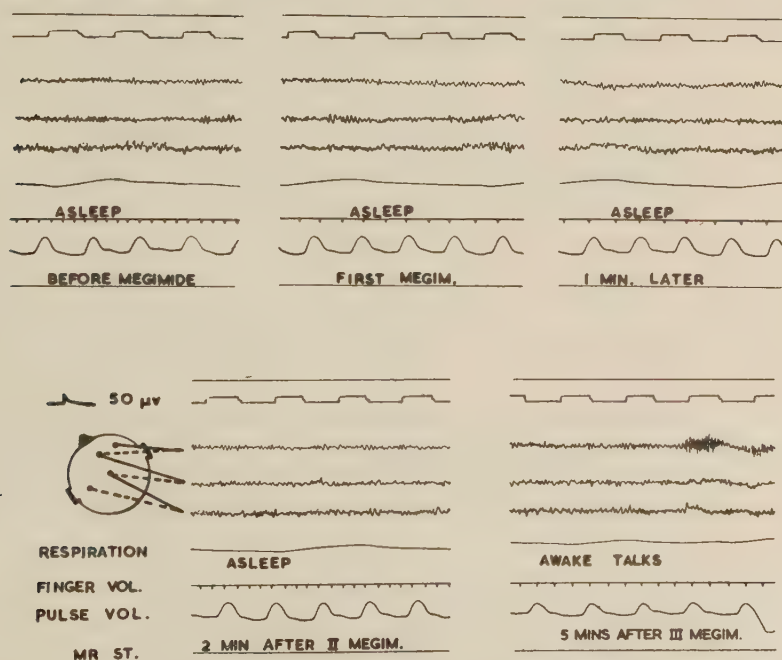


FIG. 1.—Little demonstrable E.E.G. or autonomic change during and after Megimide administrations. No reduction in fast activity following arousal.

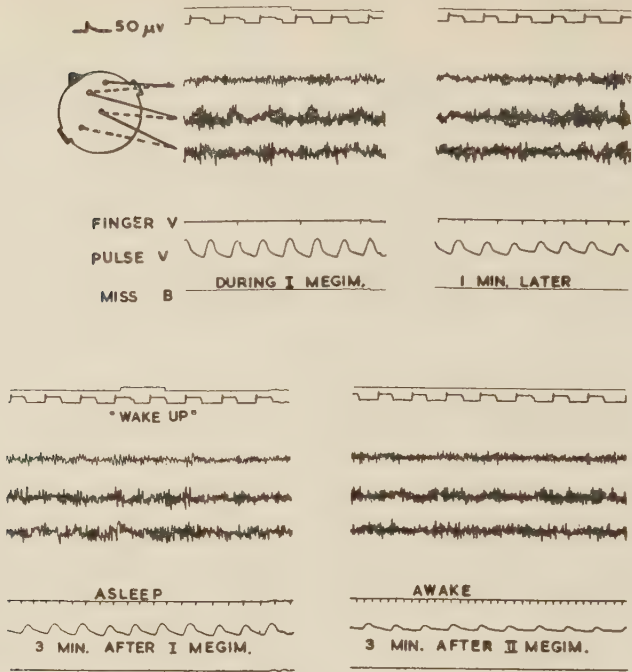


FIG. 2.—Gradual vasoconstriction during Megimide administration. Persistence of fast activity in the E.E.G.

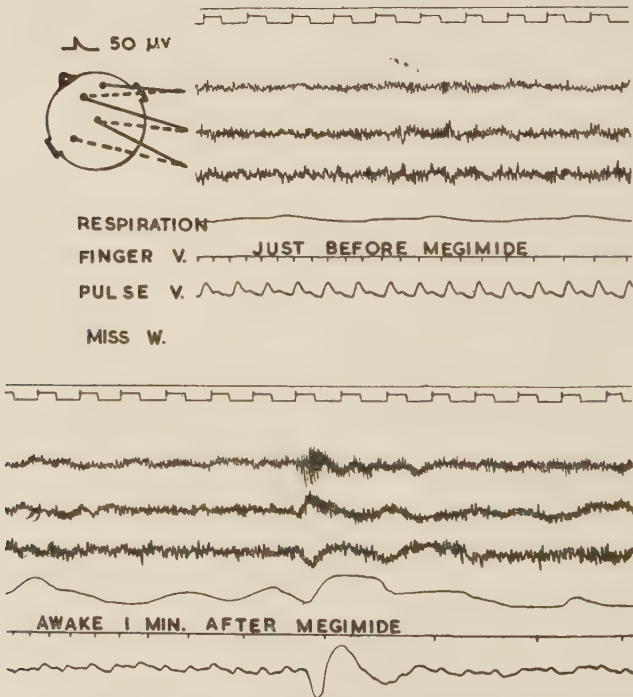


FIG. 3.—Pulse rate, pulse volume and respiratory changes following arousal. E.E.G. similar in the sleeping and waking state.

the subject a short time earlier might have been unresponsive to a similar stimulus. Awakening was not preceded by a change in the E.E.G. activity or by increasing responsiveness to stimuli as reflected either in the E.E.G. or plethysmogram. A gradual vasoconstriction, however, developed in many cases resulting in the pulse amplitude usually being much smaller prior to awakening than at the onset of sleeping (Fig. 2). Awakening was generally accompanied by further vasoconstriction and a change in the pulse rate and respiration. However, there was often remarkably little difference between the E.E.G. pattern just before and after awakening unless much slow wave activity was present during sleep, in which case the latter activity largely disappeared (Fig. 3). The administration of Megimide did not appear to cause any significant reduction in the E.E.G. barbiturate fast activity (Figs. 1, 2 and 3). No spikes, sharp waves or complex wave forms appeared after a maximum of 150 mg. of Megimide. After arousal the subject would usually doze or sleep again but would easily awake to a further stimulus.

### CONCLUSION

The persistence of barbiturate fast activity in the E.E.G. after arousal does not support the hypothesis of a direct pharmacological antagonism of Megimide towards barbiturates. The absence of E.E.G. and vasomotor changes immediately following Megimide administration or prior to awakening provides no further help in deciding the site of action of the drug. In our subjects arousal was sudden and usually followed a verbal stimulus which a short while previously had been ineffective. This suggests that arousal following Megimide administration is an expression of increased responsiveness rather than due to direct stimulation.

This view is in keeping with present clinical practice, for in barbiturate intoxication the aim of treatment with Megimide is not to stimulate the return of consciousness but rather to restore reflex activity, enabling the patient to be maintained in a physiological "safe" state.

### ACKNOWLEDGMENT

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# HYDROXYZINE (ATARAX) IN THE RELIEF OF TENSION ASSOCIATED WITH ANXIETY NEUROSIS AND MILD DEPRESSIVE STATES

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## INTRODUCTION

TURLE (1) in a double-blind trial using hydroxyzine found that of 18 patients admitted to a neurosis unit (7 anxiety neurosis, 1 obsessive-compulsive state, 6 depressive states and 1 involuntional melancholia) only 3 patients showed signs of improvement on a dosage of 30 mg. by mouth, t.d.s. Only 1 out of 8 selected on account of tension symptoms was relieved. The other 2 improved cases were depressive cases with secondary anxiety features. He concluded that the drug was of no manifest benefit in neurotics. The serene tension-free effect reputedly produced by the drug and described by American workers was not observed.

Seneca (2) claimed that in his trial all cases of anxiety, nervousness, apprehension and functional nervous disorders showed adequate response with treatment from 4-6 weeks, on 10-25 mg., 2-4 times daily.

The authors report a series in which Turle's disappointing results in tension states appear to be confirmed.

## PHARMACOLOGY

Hydroxyzine is said to be of value for its tranquillizing effect in acute and chronic emotional disturbances of either psychogenic or organic origin in which there is a tension component.

The drug is chemically related to the anti-histamines and has the chemical description, 1-p-chlorobenzhydryl-1-4-(2 hydroxy-ethoxy) diethylenediamine dihydrochloride. Although hydroxyzine has a central action, supposedly by depressing the reticular formation in the brain stem, narcotic and hypnotic effects are minimal at therapeutic dosages.

## CLINICAL MATERIAL

Thirty-seven patients were selected for the trial because they complained of tension within the setting of an anxiety neurosis, depressive or mixed depressive-anxiety state. Some of the female patients were in a neurosis unit and the rest were from out-patients.

## METHOD

The makers' recommended dose when the trial began was 2, 10 mg. tablets, t.d.s., and this was used throughout.

In a double-blind trial over a four-week period, bottles with a fortnight's supply of either active substance or placebo were marked with a cypher by the dispenser. It was arranged that half the patients would commence the trial on placebo in an attempt to avoid carry-over effect. (Raymond *et al.*) (3).

## CLINICAL ASSESSMENT

Each patient received a form on which they were told to make daily records of their own assessment of the effects of hydroxyzine which was being given specifically for the relief of tension.

The following signs were to be used, ++ = very good effect, + = good effect, O = no effect, - = poor effect and -- = very poor effect. Instructions also included requests to comment on any new symptoms which appeared whilst the drug was being taken and whether symptoms other than tension were relieved by it. They were asked to complete the 4 weeks trial whatever the effects even if it meant reducing the dosage themselves.

## RESULTS

Only 20 forms were adequately completed, of which 9 were males and 11 females. Ten had begun on placebo and 10 on hydroxyzine. By inspection, as forms were returned, it was soon apparent that there was a high frequency of "no-effect" responses and few "very good effect" or "very poor effect".

Newer, non parametric, statistical methods were used, being more suitable for small samples as here (4).

Signs were allocated values as follows, ++ = 2, + = 1, O = 0, - = -1, -- = -2. By the Dixon and Mood (1946) sign test there was no significant difference between drug and placebo.  $\chi^2$  for hydroxyzine = 14.6 and was significant at the .01 level of confidence. With placebo  $\chi^2$  = 13.13 being significant at the .05 level of confidence and very close to the .01 level. (P = 13.27 for 4 degrees of freedom at .01 level of confidence.) This means that the results in both drug and placebo trials did not occur by chance but, as the sign test showed, significance was not due to the activity of hydroxyzine or placebo. Further investigation of other variables was indicated.

Fifteen patients only completed half the trial on either drug or placebo. By inspection it was quite obvious that scores followed the same pattern as for those statistically treated.

## DISCUSSION

A tranquillizer claimed to have no hypnotic or narcotic action at therapeutic dosage and without side-effects of any serious consequence is worthy of careful objective clinical assessment. However, when only a particular symptom is being considered subjective reporting of its effects are in our opinion quite justified. In this trial clinical observations confirmed that the patients' recorded impressions were reasonably reliable. It soon became apparent that no dramatic effects were being produced either in respect of tension or on the intrinsic nature of the illness of which it was a symptom. The results were sufficiently disappointing to make us decide not to continue the trial on the scale originally envisaged.

Tiredness, sleepiness, drowsiness, dizziness, headaches, nausea and dryness of the mouth have been mentioned as probable side-effects of the administration of the drug. Considering all 37 of the patients in this series comments were made in one-third of all trials with placebo and in two-thirds with the hydroxyzine. One complaint of headache occurred with placebo and five with hydroxyzine. Two patients noted sleepy feelings with both placebo and active substance. Total comments of sleepiness, drowsiness or tiredness, were in a ratio of three to one in comparing drug with placebo. Nausea was noted twice with placebo and only once with hydroxyzine. The one mention of dizziness occurred during placebo treatment.

A male patient aged 39 took over 30 tablets at once and, after telling his wife some hours later, was admitted to hospital for observation. No severe narcotic or hypnotic effects were noted. The patient spoke of having felt a little drowsy and slightly weak in the legs. No toxic damage was manifest clinically. No disorder of the haemopoietic system or of liver function was seen in any patient in this trial.

### CONCLUSION

In this assessment of the tranquillizer, hydroxyzine, in doses of 20 mg.,\* t.d.s., as regards its effect on tension feelings in neurotic and mild depressive states, it is shown statistically that results were not significantly different from those of a placebo identical in colour, shape and size. Clinical observation confirmed the subjective data.

The frequency of complaints of drowsiness and headaches whilst on the active substance suggests that these are genuine side-effects.

\* In a recent private communication to one of us, the makers pointed out that "more serious cases under psychiatric supervision may require doses of 150 mg.-300 mg." It is possible that better results might have been obtained with higher dosage, even for our relatively milder cases.

### ACKNOWLEDGMENTS

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# DELIBERATE RE-HYPNOTIZATION AFTER THE PATIENT'S REFUSAL

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A CASE closely comparable with that reported below does not appear to have been described, possibly because of the ethical problems involved. Watkins (1947, 1951), in the description of two cases, has made the most nearly related contribution to the old debate as to whether an unwilling subject can be hypnotized. His cases were both trained subjects who were offered money rewards to attempt to resist the formal induction of hypnosis before an audience. They were both successfully hypnotized. The fear-inspired unwillingness of the patient to be described would appear to have been in a rather different category.

## CASE HISTORY

The patient was a 21-year-old female typist of average intelligence. She had suffered from habitual nocturnal enuresis till the age of eight and occasionally thereafter. Her chief complaint, however, was of a liability to incontinence of urine by day under conditions of excitement or under emotional tension of any kind—an extreme form of a common symptom. Her admission for psychiatric treatment was precipitated by an unfortunate example of this incontinence. She was playing table-tennis in mixed company, and during a brief break in play was lightly springing about on her toes. One of the men present asked, jestingly, "What's the matter with you? Can't you hold your water?" Such was her embarrassment that she was immediately incontinent of urine, a fact which was obvious to those present.

It was thought that she might benefit from a technique for giving increased control of urgency, using hypnosis. With this object she was interviewed by the writer, and, after a discussion of "emotional tension", it was proposed that she could be taught to relax and, by this means, control her disability. The emphasis was on relaxation and no mention of hypnotism was made.

Suggestions of relaxation were made and gradually a fairly deep trance achieved with the successful production of rigidity of limbs, analgesia of the hand and deafness. The demonstration of the control of sensation was used to explain to her how "relaxation" could help to control sensations and would be used to control bladder sensation. In order to facilitate subsequent re-hypnosis the suggestion was made that, "Whenever you sit in a chair and look at me and I clap my hands, you will immediately return to the state in which you are now". Amnesia for this suggestion was then induced to increase its likelihood of success (Erickson and Erickson, 1941). The trance was then terminated and the patient returned, after further brief discussion, to the ward.

In the course of the evening of that day the patient fell into conversation with another patient. The latter had lately been hypnotized by another psychiatrist and mentioned this fact, whereupon the other realized that she too had been hypnotized. Furthermore, the amnesia which had been intended to cover one specific suggestion, in fact covered almost the whole of the session. The patient, having only the lay person's knowledge of hypnotism, was greatly alarmed and distressed to find that she was unable to recall what had happened between the time of the initial conversation with the writer and the end of the interview. She confided her fears to the ward sister.

The next morning the patient refused to have any further treatment. She was interviewed by the writer in the presence of the ward sister and the nature of hypnotism simply explained in an attempt to reassure her. She remained quite unmoved in her attitude however, despite assurances that it was impossible to make a hypnotized person do anything if she was not willing (this is interesting in view of the subsequent happenings). She did not respond to a request to ask any questions she liked. She showed marked hostility, and when asked why, replied, "I'm frightened of you."

A considerable practical and ethical problem was obviously present. If her refusal

of hypnosis was respected, her amnesia would remain. If however, despite the ethical objections to such a course, a successful attempt to re-hypnotize her were made, her amnesia could be removed, her fears and distress relieved, and the treatment originally planned could be continued. The decision taken, rightly or wrongly, was that to leave her with a patch of amnesia associated with a fear of something unknown could have so adverse an effect upon her as to justify an attempt at re-hypnotization.

The patient was therefore interviewed later that day by another psychiatrist with the ward sister present, and a few moments after this began, the writer entered the room on the pretext of discussing an electroencephalogram. On the way out of the room the writer casually asked the patient, "Can you still not remember?" As she replied she looked at the writer, who was carrying his hands lightly together before him and who then very quietly and unobtrusively clapped his hands. The patient suddenly diverted her gaze, and continued to reply that she couldn't remember. Then she hesitated and became glassy-eyed. She said, "My mind's going all queer." A second hand-clap then accompanied the instruction, "Close your eyes and try and remember", after which a third hand-clap was made. The patient had by now entered an obvious trance.

"You can remember now."

"My arm is all stiff." Pause. "My hand" (she pinched it as in the first session).

Further explanations and suggestions were now made. "You are not frightened now are you?" "No." Asked if she would continue the treatment she assented readily. Suggestions were then made to the effect that she would have no more fear, and would indeed look forward to the treatment sessions with happiness because her disability was to be relieved. The trance was then ended, after which she appeared confused as if some further spontaneous amnesia was present.

When seen the next day she was happy, smiling and co-operative, and remained so whenever seen in the seven months which followed, except that four weeks after the original episode she stated that she still felt apprehensive before being seen. Hypnotic suggestions rectified this.

### TREATMENT

She was discharged from hospital, as she could easily be seen as an out-patient. She was seen weekly for the next six weeks and every three or four weeks thereafter.

Post-hypnotic suggestions were used to bring about analgesia of any part of the body when she said aloud, "No pain in my (hand, etc.)." Then when she just "thought" the words and finally when she "wanted" it without actually saying any words to herself. Similarly she was taught to render the analgesic part normal again at will. This removal and return of sensation was repeated many scores of times, and practised by the patient during each day till full voluntary control of the perception of discomfort in the superficial tissues was attained. After three weeks of this, post-hypnotic suggestions were given to the effect that later that day, whenever she felt the need to pass urine, she would at once voluntarily abolish the sensation causing that need, so that she would only go to the toilet at tea-time and bed-time. She was instructed not to attempt this except on that one day.

When seen the next week she reported success and further hypnotic suggestions were given—that she would be able voluntarily to abolish her sensations of urgency, and so control the desire to micturate, on all days, and at all times, in the future.

She was seen at intervals for another five months, and throughout this period reported that she now regularly micturated only three times per day, instead of a dozen times or more. Her voluntary control of pain perception also continued. She expressed herself delighted. She became engaged, got married, and left the district. An attempt to contact her later was not successful.

### COMMENT

The patient was a particularly good hypnotic subject. The present case would lend support to the view that if such a person can once be hypnotized, providing appropriate suggestions have been made during that initial trance,

then subsequent re-hypnosis can be achieved despite strongly motivated refusal by the subject. This would also probably be true with an unscrupulous hypnotist.

The eventual successful treatment of this patient justified, it can be argued, the decision deliberately to re-hypnotize her after her refusal. It is very doubtful if a successful courtship, culminating in marriage, would have been compatible with the patient's previous disability.

The achievement of voluntary control of perception of discomfort, in the writer's experience, is only occasionally as stable as in this case. It is entirely compatible with the view that to perceive is as much an active, constructive response as is a motor act which is subject to voluntary control.

The case is similar in some respects to that of a patient described by Jones (1956), whose urinary frequency and incontinence were successfully treated by a conditioning procedure. The method adopted in the present case, however, avoided the disadvantages attendant upon repeated catheterization.

#### SUMMARY

A case is described which contributes to the debate whether an unwilling subject can be hypnotized. The patient was a female who suffered from embarrassing urgency and incontinence of urine with excitement or emotional tension. She was hypnotized by explanations about "relaxation". Suggestions were given for re-entering a trance at a hand clap.

Amnesia for the trance appeared. Discovery, later, that she had been hypnotized caused great fear and despite all reassurances she refused further treatment. The ethical problem being fully considered, she was re-hypnotized, despite her refusal, by a hand clap. Suggestions dispelled her fear.

Hypnotic suggestions were used to teach voluntary control of perception of discomfort, including bladder sensations. Her disability was completely relieved during a seven month follow-up during which she pursued a successful courtship, culminating in marriage, after which contact with her was lost.

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# PHENOTHIAZINE TOXICITY, EXTRAPYRAMIDAL SEIZURES, AND OCULOGYRIC CRISES

By

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## INTRODUCTION

PROCHLORPERAZINE (Compazine, Stemetil) and chlorpromazine (Thorazine, Largactil) frequently produce tremor and rigidity. Less well known are the severe tonic spasms of the muscles of the head and neck which can result from these phenothiazine derivatives. This paper directs attention to these spasms and their similarity with "extrapyramidal seizures" and oculogyric crises.

## TONIC SEIZURES FROM PHENOTHIAZINE DERIVATIVES

Kulenkampf and Tarnow (15) were among the first to report patients with paroxysmal tonic phenomena from phenothiazine derivatives. The patients had an intermittent sensation that the tongue was about to protrude and noted tight muscles in the neck and throat. It was necessary to discontinue chlorpromazine because of this "oral syndrome".

Freyhan (8, 9) and others (Christian, 2; Delay, 3) have described patients who developed hypertonic muscles in the neck from prochlorperazine. Some of the patients had waves of generalized rigidity, bizarre postures of the head and neck, and anxiety. Two patients who had received perphenazine (Trilafon) were almost catatonic with a type of generalized "waxy flexibility", and had their necks flexed backward as though in spasm (Berry, 1). Muscle pain, hallucinations and headache have occurred in some patients.

Vertical deviation of gaze has been seen in several of these patients who had spasmodic hypertonus in the muscles of the shoulders and neck. Chlorpromazine has been previously reported to produce deviations of gaze indistinguishable from oculogyric crises.

The incidence of severe tonic reactions due to phenothiazines is unknown. Freyhan (9) records severe dyskinesia in eleven out of sixty-seven patients with extrapyramidal symptoms from prochlorperazine. The severe paroxysmal hypertonus probably is caused more often by prochlorperazine than chlorpromazine. This may be related to the high incidence, as great as 50 per cent. (Freyhan, 9; Holman, 12), of extrapyramidal side-effects with prochlorperazine therapy.

Younger patients seem more susceptible to the extreme tonic seizures caused by the phenothiazine derivatives.

The duration of the severe tonic effect from phenothiazine derivatives has been variable, but most patients are markedly improved one or two days after the drug is stopped (Durn, 5).

## EXTRAPYRAMIDAL SEIZURES

There have been occasional reports of seizures which seemed to arise from subcortical structures. Some of the terms suggested for these seizures have included "subcortical epilepsy" (Spiller, 21), "extrapyramidal epilepsy" (Sterling, 22), or "striatal epilepsy" (Wimmer, 26). These seizures usually consisted of spasmodic hypertonia of the muscles of the limbs or of the head and neck. Autonomic symptoms or unconsciousness have occurred. Several of the patients with extrapyramidal seizures had encephalitis lethargica. Wimmer states that "during the rather monotonous progression of the generalized Parkinsonian rigidity and akinesia paroxysmal tonic syndromes may now and again occur".

Recently Matthews (18) discussed four patients with tonic seizures and disseminated sclerosis. During the tonic seizures the posture of the limbs closely resembled tetany, and there was severe pain in the affected limbs. The seizures were of rapid onset, brief duration and great frequency. There is little exact pathologic evidence in these or other cases of tonic seizures, although in some reports mentioned by Matthews, lesions were present in the subthalamic area.

## OCULOGYRIC CRISES

Seizures from extrapyramidal structures are admittedly atypical, and their actual existence has been questioned. Oculogyric crises on the other hand have been well described and are familiar to most clinicians. The term oculogyric crises describes a group of spasmodic eye deviations which are most often directed vertically, and which last for minutes or hours.

The extensive review by Jelliffe (13) records many patients with oculogyric crises who also had paroxysmal anxiety or a sense of impending doom, tachycardia, crying spells, headaches, and compulsive thoughts with or without hallucinations. Lemos (16) described associated masticatory and glossopalatolaryngeal spasms and spasms of the arms. F. B. Walsh (24) states that in oculogyric crises "the head is usually thrown back and not infrequently the mouth is held open and the tongue may protrude". McCowan and Cook (19) say that "the crises are in the nature of tonic seizures and need not be confined to the eye muscles, a more or less co-ordinated spread to the muscles of the head and neck being not uncommon". Many patients with oculogyric crises have had increased tone in the muscles of the head and neck, generalized hypertonus or axial torsion.

There have been infrequent reports of oculogyric crises associated with brain tumours, manganese poisoning and other diseases, but oculogyric crises have been considered almost pathognomonic of encephalitis lethargica (Duke-Elder, 4). The crises are more likely to occur in youthful patients with encephalitis than in the older ones.

The pathologic changes in patients with oculogyric crises are similar to those in other patients with encephalitis lethargica. Various authors have emphasized the lesions in the basal ganglia, including those in the corpus striatum and subthalamus. McCowan and Cook (19) stated that the lesion "lies in associational mechanisms situated above the four supranuclear centres subserving conjugate movements", but no more specific localization was possible.

The physiologic aetiologies which have been proposed have included paroxysmal vasomotor changes, relaxation of cortical inhibition, or irritation of the oculomotor centres. No one physiologic or pathologic basis for oculogyric crises has been generally accepted.

Precipitating factors for individual crises include fatigue or psychic trauma, and suggestion can either precipitate or abort an attack.

### TREATMENT

Lowering the dose of phenothiazines or the use of anti-Parkinsonian drugs usually has been sufficient treatment for the mild Parkinsonism due to the phenothiazine derivatives. In fact, the extrapyramidal side-effects have been called a guide to adequate dosage (Goldman, 10; Holman, 12), and therapy of the mild tremor and rigidity is often unnecessary. On the other hand, treatment of the acute severe motility disturbances caused by phenothiazines may be difficult, especially if suspicion of hysteria or central nervous system injury obscures the correct diagnosis.

There are few leads to treatment of the tonic seizures due to phenothiazines that can be found in the reports of extrapyramidal seizures or oculogyric crises. Treatment of the scattered cases of extrapyramidal seizures has been indefinite and unsatisfying. Treatment of oculogyric crises has also been disappointing. Hyoscine or other belladonna derivatives, amyl nitrate, and the newer anti-Parkinsonian drugs have been only moderately successful. Klemme's (14) operative removal of the premotor cortex at the junction of the first and second frontal convolutions has been only occasionally done. Chemopallidectomy may prove to offer significant amelioration of the crisis.

The frequency and severity of oculogyric crises may be lessened by rest and a bland environment. Lying down shortens the crises for some patients and oculogyric crises disappear during sleep.

Adrenaline and caffeine are reported to decrease the severe motility disturbances due to phenothiazines, but there is no explanation of their beneficial effect (Durn, 5; Freyhan, 9). The use of amobarbital sodium (amylobarbitone, Amytal) to induce sleep was effective in one patient with tonic seizures from prochlorperazine (Christian, 2). Amytal previously had been reported to mitigate somewhat the autonomic seizures of a patient who had encephalitis lethargica (Ostow, 20).

### COMMENTS

The sequelae of encephalitis lethargica include many muscular, psychic and autonomic responses; and most of the neurologic complications from phenothiazines are within the range of post encephalitic Parkinsonism. Although the tonic seizures from phenothiazines are only one more of the extrapyramidal complications of these drugs, their occasional severity and their resemblance to the disputed extrapyramidal seizures and to oculogyric crises makes these tonic phenomena of special interest. Furthermore, observation of the neurological effects of phenothiazines may elucidate features of post-encephalitic Parkinsonism, just as the appearance of encephalitis lethargica directed attention to subcortical neurophysiology.

The pharmacological data on the phenothiazines do not yet explain the production of Parkinsonism by these drugs. Monkeys which are given chlorpromazine can have signs of toxicity which are similar to those in man. Essig and Carter (6), using doses of chlorpromazine as high as 77 mg./kg. reported bizarre searching behaviour suggestive of hallucinations. In two of the monkeys prominent movements of the head and eyes resembling oculogyric crises and retrocollic spasms were observed.



The primary locus of the central nervous system action of phenothiazines is not entirely clear. A recent article by Vogt (23) reviews evidence of an effect of chlorpromazine on the reticular system in particular, but also an effect on the limbic system and posterior hypothalamus. Though studies of the localization of chlorpromazine are being done with radioactive isotopes, the results are not yet available (Durn, 5).

The extrapyramidal symptoms caused by encephalitis lethargica are sometimes attributed to overactivity of cortical areas in the absence of adequate suppressor or modifying effects by the diseased basal ganglia. Decrease in inhibitory influences on fibre tracts, or "release" phenomena, are among the suggested pathophysiologic bases of post-encephalitic Parkinsonism. The fact that phenothiazines can reproduce these extrapyramidal symptoms does not necessarily imply that these tranquilizers actually exert their effect through a reduction of inhibitory influence on cortical fibre tracts. If this were true, then the "arousal" response on EEG, which Wilson and Glotfelty (25) have shown to be blocked by some phenothiazine derivatives, might appear to represent a reflection of inhibitory activity. The local effects of phenothiazines are probably numerous, and the end result of these effects may vary in different parts of the brain.

The permanent effects of the phenothiazine derivatives on the human brain are unknown. The fact that the neurological signs of the phenothiazine toxicity are transient suggests, but does not prove, that these drugs do not cause permanent local lesions. There are other drugs which have been reported to injure specific areas of the brain. For example, Hoffman (11) found marked loss of Purkinje cells in the cerebellum of a patient who received parenteral diphenylhydantoin phenytoin (Dilantin) for severe epileptic convulsions. The anti-metabolite 3 acetyl-pyridine can selectively destroy neurons in a specific hippocampal area (MacLean, 17). For chlorpromazine itself, Fallik and Treves (7) describe a patient who developed a left hemiparesis and disturbances of the left V, VII, X and XII cranial nerves after 2355 mg. of chlorpromazine given over a twelve-day period. The patient was well within two weeks after medication was discontinued.

When used in therapeutic doses, the phenothiazines may never permanently injure the central nervous system. Their innocence may, however, be difficult to prove to a patient who develops idiopathic Parkinsonism years after having had identical symptoms as a side-effect of tranquilization.

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# ADMISSION TO MENTAL HOSPITAL AFTER THYROIDECTOMY—OBSERVATIONS ON A SERIES OF CASES

By

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THIS paper describes a group of female patients admitted to mental hospital who in the past had undergone thyroidectomy for thyrotoxicosis. It was thought that a group of this kind who had been admitted might show, possibly in an exaggerated form, the personality features said to be common to individuals predisposed to thyrotoxicosis. The series does not include any toxic psychosis attributable to the disease itself and the title may possibly be misleading in this respect. Most psychiatric studies have dealt with the patient at the time of the illness and the emphasis has tended to be on precipitating factors. A much quoted study is that of Conrad (1) (1934). As a psychiatrist working in a thyroid clinic she described 57 cases referred for psychiatric opinion and used 48 cases not so referred as controls. She concluded from a careful study that the onset of the illness was due to two main patterns of emotional disturbance: (1) fear of loss of shelter and affection equivalent to deprivation of mother, (2) fear of dangers of the mother role. She found a large number of cases where there had been loss of the mother at an early age. Ham, Alexander and Carmichael (1951) (2) remind us that the disease occurs spontaneously only in man, not animals, and rarely in primitive communities. They describe a "specific dynamic pattern" in thyrotoxicosis, viz., Frustration of dependent longings and persistent threat to security (exposure to death and other threatening experiences in early life, *causing* unsuccessful premature attempts to identify with the object of the dependent cravings. There is a continued effort toward premature self sufficiency and to help others. These strivings for self sufficiency and taking care of others fail causing thyrotoxicosis. Lidz and Whitehorn (1949) (3) also regard thyrotoxicosis as following in almost every case a somewhat similar pattern. They regard these patients as a group less wanted than their sibs but eventually achieving parental affection by being "good children" (in the exaggerated sense) and persist in this pattern of behaviour in adult life. They expect the same unswerving fidelity they gave to their parents in return for excess of affection that they give to a parental figure. These authors claim that this almost invariable pattern provides short cuts in therapy, e.g., when the illness arises soon after marriage, problems are apt to revolve about difficulties in leaving the parental home. Working on different and more objective lines Ruesch (4) and his colleagues at the Thyroid Clinic of the University of California studied 43 patients carefully selected to give a fair representation of patients treated by thyroidectomy. They verified thyrotoxicosis by histological reports on the excised portion of the gland. Each patient had 5 interviews and abbreviated Wechsler and Minnesota Multiphasic Personality Inventory Tests. Their main interest was the prolonged psychological invalidism which had been noted to



immediately follow operation. They found that patients with delayed recovery tended to have a long record of previous hospitalization, and a high frequency of major and minor operations. In the M.M.P.I. the most common pattern was "undifferentiated normal". They concluded that patients with thyroid disease are not entirely normal sociopsychologically, but the group could be subdivided into two entities: (1) normal or almost normal, (2) hysterical or anxious type in female patients, or dependent personalities in male patients.

Murray (1950) (5), a physician writing from the Victoria Infirmary, Glasgow, emphasized the importance that emotional factors played in deciding the response to treatment especially to anti-thyroid drugs. He also expressed the view that "examination of the psychological aspects (of the patient) should be made before any decision is made on thyroidectomy as it might sometimes be possible to improve the patient without operation while it might sometimes cause rejection as unsuitable of those cases which subsequently relapse and which then prove so difficult to control with thiouracil.

This series consists of thirteen female patients admitted to the Park House Villa of Hellingly Hospital during a predetermined period 1 November 1956-1 November 1957. In the case of 8 patients it was the first admission. They all gave a history of having undergone at some time in the past thyroidectomy for hyperthyroidism. The hospitals performing the operation were widely spread, 1 in Germany, 1 Women's forces, 5 different London teaching hospitals, 6 different provincial hospitals. In only seven cases was it possible to obtain notes from the hospital where the operation had been performed. In four cases histological examination had been undertaken, which confirmed toxic changes in 3 cases and was doubtful in the remaining one. Nothing in the clinical notes suggested any doubt about the diagnosis. Where the notes were unobtainable this was usually due to loss of records in war-time and there would appear to be no obvious reason for regarding this group as different from the others. There were no cases of recurrence of thyrotoxicosis. All the patients were examined by Mr. Bevan, the Senior Psychologist, and a detailed history taken by myself. *Ages* of the patients were 26, the youngest, 3 in the 30's, 3 in the 40's, 2 in the 50's, and 4 in the 60's, the oldest being 69. *The incidence* was high, the total of admissions for the year was 391 so that almost exactly one patient in 30 had a thyroidectomy scar. It is not possible to assess what proportion of thyroidectomized patients come under psychiatric care by studying admissions as there are no reliable figures for the incidence of the operation or the disease in the general population.

Psychiatric diagnoses, which were arrived at by myself and one of the consultant staff in each case, were:

|                                                                              |   |
|------------------------------------------------------------------------------|---|
| psychopaths—one primarily alcoholic—                                         | 2 |
| inadequate personality                                                       | 2 |
| anxiety state                                                                | 2 |
| involutional depression                                                      | 6 |
| (3 with lifelong history of neurotic behaviour) obsessional ruminative state | 1 |

That is they tended to fall into the neurotic group. Of the 391 admissions for the year the bulk of 231 were labelled "depression"; because of different psychiatrists attending different patients no uniform analysis into the types of depression could be made accurately. The other admissions were schizophrenia 48, mania 6, senile and presenile dementia 12, neurotic 36 and psychopaths 10. These represent the bulk of admissions to Hellingly, but there is a separate ward

to take senile patients and another ward taking a small number of severely disturbed patients; unfortunately these were not studied. Of the 36 primarily neurotic patients 5 were thyroidectomized but it would be misleading to deduce such a high incidence as probably many of the patients labelled depressive were essentially neurotic. None of the schizophrenic patients were thyroidectomized, and amongst the large chronic population of the hospital (c. 800) consisting mainly of schizophrenics I was able to find only one thyroidectomy scar.

*Relationship of the operation to the onset of psychiatric symptoms*

The operation was before the onset of psychiatric symptoms in 9 cases in periods from 5 to 27 years (5, 6, 7, 8, 12, 14, 15, 22, 27). The operation took place during the course of psychiatric symptoms similar to those causing admission in 4 cases (1 had been admitted twice for involutional depression and another had received out-patient psychotherapy for an anxiety state). One patient came to hospital three weeks after operation suffering from involutional depression the symptoms of which had been present three months before admission to hospital. Nine patients felt subjectively better and 4 worse after operation. Of the 4 who felt worse one had previously been admitted but the other 3 had not had psychiatric care. There was a tendency to psychiatric chronicity, as suggested by the diagnosis, but this is probably as typical of the psychiatric diagnosis as any feature of the thyroid personality. Psychological testing was carried out on all patients except one of the psychopaths who refused. On the Wechsler scale 8 patients were of average intelligence, 3 of low average and 1 of high average. The Minnesota Multiphasic Personality Inventory was not valid in 4, suggested no abnormality in 2 and suggested neurosis in 4 and hypomanic in 1 of the psychopaths. (Ruesch obtained similar profiles). As suggested by the diverse diagnosis there was no evidence of a *uniform psychopathology* such as premature and unsuccessful assumption of the maternal role (Ham, Alexander and Carmichael) or affecting to be good children (Lidz and Whitehorn) and not one patient could be fitted into the latter pattern of forming exaggerated and overbinding attachments, but it is probably true to say that the idea of uniform psychopathology for any one given psychosomatic illness is generally being abandoned. There was, however, a high incidence of disturbed upbringing. There were 3 cases of illegitimacy, 1 patient lost her mother at 5 years, another her father at 8; there was one case of parental separation, and one case of gross overt parental rejection. There was a high incidence of other major illness and operations. Two patients had undergone hysterectomy, and 1 irradiation of ovaries for menorrhagia. One had ankylosing spondylitis. Two wore deaf-aids, both having chronic otitis media. One patient (at 37) suffered from hypertension, sufficient to require hypotensive drugs.

## DISCUSSION

Study of this small group shows some interesting features. Their illnesses tend to fall in the neurotic and psychopathic group, and they show a high incidence of disturbed childhood background and other illnesses. The examination of this particular group has the obvious limitation that one cannot tell how typical they are of thyrotoxic patients as a whole (though as an opinion I would submit that they probably are typical); it does however have the advantage of seeing the patients a long time after the operation and the possible immediate emotional emergency which precipitated it. There remains a great need for the study of this among other problems of psychosomatic medicine, and of a widen-

ing of the clinical approach by bringing the psychiatrist in routinely rather than where everything else had failed; in not one of my cases was a psychiatrist consulted, though 4 patients had a clear history of psychiatric symptoms before operation and 2 had had some treatment. Where psychiatric help is routinely invoked in thyroid clinics it usually takes the form of superficial psychotherapy and has been shown to help, this despite the tendency to chronicity and the apparent self sufficiency of surgical and other treatments. Thus Murray, describing his work in association with a psychiatrist Dr. Adam Milne, states that "the emotional problems may be difficult to solve and the thyrotoxic symptoms be kept in control only by continued therapy. Nevertheless the discovery of the psychological disturbance may explain why a patient is unable to abandon thiouracil without relapsing and make it possible to give at least some advice and guidance which may prove beneficial. Lidz and Whitehorn writing from the Johns Hopkins Thyroid Clinic describe their work as "raising the morale of the clinic". These claims are modest, which supports their realism; with increasing experience in the psychiatric approach there is an increased possibility of therapeutic usefulness. I would like to finish with a plea for integration of psychiatry into medicine. Addressing psychiatrists this might seem like preaching to the converted, but as a group we tend to reject medical problems much as other physicians reject psychiatric ones.

#### SUMMARY

A group of 13 female patients admitted to a mental hospital who in the past underwent thyroidectomy for thyrotoxicosis is described. Their psychiatric diagnosis tended to be in the neurotic group. There was a high incidence of other illnesses and disturbed childhood background. There was no evidence of a uniform psychopathology.

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# THE PREDICTIVE VALIDITY OF A PSYCHOLOGICAL TEST OF BRAIN-DAMAGE

By

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A PSYCHOLOGICAL test of brain-damage, shown to be valid in discriminating between unequivocal brain-damaged and non-brain-damaged psychiatric patients, is limited in its diagnostic role until studies can demonstrate its independent diagnostic contribution in the clinically doubtful case of brain-damage.

A recent study (Walton and Black, 1957; Walton, 1958a) reported the validity of a new learning test (M.W.L.T.) for diagnosing organic brain-damage. Important differences in the speed of learning previously unknown verbal material were demonstrated between a combined group of 223 co-operative non-brain-damaged psychiatric patients and normal controls, and a group of 46 brain-damaged patients. The non-brain-damaged subjects included 57 normals (nurses), 125 neurotics, 30 psychotics and 21 mental defectives. The organics were mainly suffering from general cortical damage of the type found in the organic dementias and in cases of general paralysis. Of the 46 organics, 93·5 per cent. scored at or above an optimum cut-off point, whilst only 3 or 6·5 per cent. scored below that point. Of the functionals, 99·57 per cent. scored below the cut-off point. No normal control returned a high score. Only one mental defective out of the group of 233 normals and functional patients was misclassified as brain-damaged. For details of administration and scoring the reader is referred to the original publication of the test (Walton and Black, 1957).

In an effort to cross-validate these findings, a further 304 patients and normal controls were tested (Walton *et al.*, 1959a; Walton and White, 1959b). The two major conclusions of the validation study were confirmed.

1. The test appeared capable of differentiating with a negligible degree of misclassification organics with general cortical damage from functionals and normals. None of the 181 normals, neurotics or psychotics were misclassified. Sixty-six (85 per cent.) of the 78 organics were correctly identified. Thus, of the 259 patients tested in these four groups, 247 or 95 per cent. were correctly diagnosed. The original validation data for these same groups, combined with the cross-validation results of the normal, neurotic, psychotic and organic patients represents a normal and patient population of 517 subjects. Five hundred and two of these subjects, both brain-damaged and otherwise, were correctly identified.

2. Although age, intelligence and vocabulary were found to exert some influence on the test scores this was not sufficient to produce "organic" scores independently of the presence of organicity.

Two studies have also tentatively demonstrated the predictive validity of the test when applied to psychiatric patients over 65 (Walton, 1958b, c). The M.W.L.T. was administered to 48 senile psychotics in 1955, though the test results were not examined in relation to diagnosis until a two-year follow-up had been completed. Eleven of the thirteen changes in diagnosis within that two-year follow-up were correctly predicted. Forty-five of the forty-eight cases were also correctly identified when the 1957 diagnosis (including the 13 changes in diagnosis) were compared with the M.W.L.T. results obtained in 1955.

In order to confirm the apparent predictive value of the M.W.L.T., and thus to establish the independent diagnostic contribution of the test, the present study was undertaken.

#### METHOD

Sixty-six patients were referred to the psychology department in order that the psychologist should give an opinion with regard to the presence or absence of brain-damage. The M.W.L.T. was administered to each patient. The test results were not examined in relation to diagnosis until the psychiatrist had reached a firm diagnostic decision. This decision depended upon various confirmatory criteria such as: treatment confirming the absence of brain-damage (e.g. a complete clearance of symptoms following electro-convulsant therapy); neuro-surgery having demonstrated or failed to demonstrate brain-damage; laboratory tests having confirmed the presence or otherwise of, for example, G.P.I.; or evidence of unequivocal cerebral damage following head injury.

In order to provide a further check on the presence of organicity and to obviate the possibility of a spuriously high test validity (the psychiatric and psychological criteria of diagnosis may have overlapped), eight additional criteria were applied to those cases where unequivocal criteria of the type listed above were not available. The objective criteria were unrelated to cognitive or memory function (Shapiro *et al.*, 1956). The relevant information on these eight points was taken from the case-notes. The signs were:

1. Cerebral incidents or attacks, that is to say, a history strongly suggestive of focal cerebral disorder, including fits, transitional paresis and the like.
2. Confusional episodes, that is to say, episodes of abnormal behaviour and psychotic experiences in a setting of disorientation.
3. Incontinence, except if occurring only at the height of the illness.
4. Character change, such as deterioration of personal habits and/or caricaturing of previous personality traits: e.g. increased preoccupation with money, health and so on.
5. Confirmed neurological signs or symptoms, including aphasia.
6. Perplexity, that is to say, an impression or complaint of bewilderment or puzzlement.
7. Grossly abnormal EEG.
8. Presentation of a clinical picture not clearly belonging to one of the recognized "functional" psychiatric syndromes, e.g. depression with schizophrenic symptoms and visual hallucinations.

Nine cases were rejected because the diagnosis was still in doubt or had not been reached by means of criteria which were independent of functions measured by the M.W.L.T. A diagnosis of brain-damage was acceptable as

such if any of the confirmatory criteria were applicable. If none were relevant a patient was still considered brain-damaged if any of the eight objective criteria applied. If none of these two sets of criteria applied yet the diagnosis was of brain-damage, that patient would have been omitted because of the possibility that the psychological test results had influenced the psychiatrist in reaching his diagnosis.

### RESULTS

Table I shows the distribution of M.W.L.T. scores for each of the final diagnostic groups. It is apparent that none of those patients finally diagnosed as either neurotic or psychotic was misclassified. All scored at or below a cut-off point of 25. This is an important finding, for in the validation and cross-validation studies of the M.W.L.T. the optimum cut-off point for brain-damage was in fact found to be twenty-six. Of those patients finally diagnosed as suffering from generalized cortical damage, 18 or 81 per cent. scored at or above 26. All the epileptics behaved as non-brain-damaged patients. One brain-damaged patient suffering from damage in the fronto-parietal region only was misclassified. Another patient with a circumscribed lesion in the right occipital lobe was correctly identified.

TABLE I

*Distribution of M.W.L.T. Scores for Each of the Final Diagnostic Groups*

| M.W.L.T.<br>Score | Neurotic<br>Dys-<br>thymics | Neurotic<br>Hysterics | Psy-<br>chotic<br>Depres-<br>sives | Schizo-<br>phrenics | Epi-<br>leptics | Organics<br>(general-<br>ized<br>cortical<br>damage) | Organics<br>(local-<br>ized<br>lesions) |
|-------------------|-----------------------------|-----------------------|------------------------------------|---------------------|-----------------|------------------------------------------------------|-----------------------------------------|
| 1- 5              | ..                          | 5                     | 1                                  | —                   | 4               | 1                                                    | —                                       |
| 6-10              | ..                          | 4                     | 4                                  | 2                   | 1               | 2                                                    | 1                                       |
| 11-15             | ..                          | 3                     | 1                                  | —                   | 1               | 2                                                    | 1                                       |
| 16-20             | ..                          | —                     | —                                  | —                   | —               | 1                                                    | 1                                       |
| 21-25             | ..                          | 1                     | 1                                  | —                   | —               | 1                                                    | 1                                       |
| 26-30             | ..                          | —                     | —                                  | —                   | —               | 4                                                    | —                                       |
| 31-35             | ..                          | —                     | —                                  | —                   | —               | 4                                                    | —                                       |
| 36-40             | ..                          | —                     | —                                  | —                   | —               | 1                                                    | 1                                       |
| Over 40           | ..                          | —                     | —                                  | —                   | —               | 9                                                    | —                                       |
| N=57              | ..                          | 13                    | 6                                  | 3                   | 6               | 5                                                    | 22                                      |
|                   |                             |                       |                                    |                     |                 |                                                      | 2                                       |

The results provide confirmation of the predictive validity of the test, at any rate when brain-damage is of a general order. The findings from the first predictive study, involving a two-year follow-up (Walton, 1958b, c) are also confirmed. In that study 45 (93 per cent.) of the 48 senile psychotics were correctly diagnosed when the M.W.L.T. (1955) results were compared with the final diagnosis in 1957. In the present study some 82 per cent. of the cases were diagnosed correctly. If a comparison is made, however, between the results from non-brain-damaged psychiatric patients and those suffering from generalized damage (i.e. omitting the five epileptics and the 2 organics with specific lesions) 46 (92 per cent.) of these 50 cases were diagnosed correctly. Thus, an almost identical degree of differentiation has been obtained in the two independent predictive studies. This differentiation is of such a high order as to recommend the test for further cross-validatory and predictive studies.



## SUMMARY

Previously both validation and cross-validation studies of the M.W.L.T. have employed cases of unequivocal diagnosis.

In this paper is reported the degree of success obtained when the M.W.L.T. was used as a predictive instrument on cases referred to the psychologist for an opinion as to presence or absence of brain-damage. The opinions then given have been subsequently verified by means of certain criteria, which are described. Cases have been rejected where such criteria are absent or where the psychiatric diagnosis has been manifestly reached as a direct result of psychological testing.

The results are sufficiently encouraging as to permit the tentative use of the M.W.L.T. in a predictive context.

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# A CONTROLLED STUDY OF THE EFFECTIVENESS OF TRIFLUOPROMAZINE HYDROCHLORIDE

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VESPRAL, chemically designated as 10-(3-dimethylaminopropyl-2-trifluoromethyl)-phenothiazine hydrochloride\*, or trifluopromazine hydrochloride is a new ataractic drug which has only recently become available in this country. A clinical field trial with Vespral has been reported in a previous issue of this journal (1). It was then suggested that the drug was most effective in the treatment of psychotic disorders, schizophrenia in particular. The aim of this study was to evaluate, with some claim to objectivity, the effectiveness of the administration of trifluopromazine hydrochloride on the behaviour of a small population of chronic schizophrenic patients.

A placebo control group was used in a "double-blind" designed experiment. Before and After measures were made, using a simple ten-item psychiatric rating scale of our own devising, together with the Mill Hill Vocabulary Scales and a sorting test derived from the Goldstein Tests (2).

## METHOD

### *Population*

Some twenty-eight schizophrenic patients of clear-cut diagnosis were screened with the Mill Hill Vocabulary tests to exclude any possible defectives. From these patients, twenty were selected who were all functioning at a minimum grade IV level. These twenty patients were then sub-divided into two matched groups A and B of ten patients each.

There was no disagreement between psychiatrists in the hospital as to the "label" of schizophrenia attached to these patients. There was, however, some difference of opinion as to the sub-groups into which they could be classified. The general opinion was that the experimental population was made up of eight paranoid type, four simple type and eight mixed type. All patients were seriously disturbed, the majority had delusional ideas and many were also actively hallucinated.

Each member in group A had a partner in group B. These pairings were made on the criteria of (i) Age, (ii) Duration of stay in hospital, and (iii) each patient had a partner of similar schizophrenic type. The resulting groups contained nine males and one female in group A, and seven males and three females in group B.

Following the commencement of the trials, and before the end, one patient from each group left the hospital. This necessitated matching the remaining partners with each other for final evaluation. Fortunately, these individual patients were of the paranoid type, and of an age difference of only three years.

\* Experimental tablets were kindly provided by Messrs. Squibb & Co.

|             | Mean Age |        | Age Range |        | Mean Duration of Hospitalization |        | Length of Stay |        |
|-------------|----------|--------|-----------|--------|----------------------------------|--------|----------------|--------|
|             | years    | months | years     | months | years                            | months | years          | months |
| Group A . . | 45       | 5      | 30        | 5      | 10                               | 3      | 1              | 6      |
|             |          |        | to        |        |                                  |        | to             |        |
|             |          |        | 58        | 8      |                                  |        | 20             | 5      |
| Group B . . | 47       | 3      | 32        | 10     | 11                               | 1      | 1              | 8      |
|             |          |        | to        |        |                                  |        | to             |        |
|             |          |        | 58        | 6      |                                  |        | 21             | 0      |

### Measures

All patients were first scored on a ten-item rating scale. Each item could be rated on a 0-5 point scale. Three items were concerned with effect or emotionality; namely, hostility, social relationships and general emotional tone. Three items were concerned with the psychotic process more directly; namely, delusions/hallucinations, sense of reality and insight. The remaining four items were concerned with general ward activities: namely, initiative, cleanliness, useful work and general motor activity.

The sorting test was then administered to all the patients. This test produced three scores for each patient: (i) Acceptable sortings, i.e. sortings for criteria which arbitrarily may be regarded as reasonable; (ii) Non-acceptable sortings, groups made up for a bizarre or non-acceptable reason; (iii) The average time taken to produce each sorting.

### Dosage

After the completion of the testing and the initial ratings of all patients, a course of tablets was commenced. Those patients in group A received tablets from bottles labelled A, and group B received tablets from bottles labelled B. All the "A" tablets were of the same type and vice versa. However, tablets A and B could not be visually distinguished from each other. Only the hospital pharmacist knew that in fact the A tablets were placebo and the B tablets were the drug.

All patients began with one tablet t.d.s. for three days (i.e. 10 mg. drug t.d.s.) then one tablet t.d.s. for the next five days (i.e. 25 mg. drug t.d.s.) and finally, they received two tablets t.d.s. for fifty-four days (i.e. 50 mg. drug t.d.s.), making a total of sixty-two days in all for the trial.

### RESULTS

The following points emerged when the results obtained from repeating the various measures as were administered at the outset, were subjected to statistical analysis.

All three parts of the Psychiatric Rating Scale showed a significantly greater improvement among the treated group than among the untreated. Those items concerned with Affective Tone revealed that the treated member of each matched pair showed a greater difference between initial and final rating than his untreated partner. Further, the treated group as a whole showed a significantly greater improvement than the control group. It was noted that the variation between the partners in a matched pair was significantly less than the variation between matched pairs, showing that the pairings were effective in producing a more precise comparison. It was clinically evident that the majority of the treated patients became more sociable, less hostile to both staff and fellow patients and generally appeared to be happier and less withdrawn.



Similarly, the other two parts of the Psychiatric Rating Scale revealed a significant improvement among the treated group. Those patients belonging to the drug group showed a reduction in their frankly psychotic symptoms. At the end of the trial several of these patients spontaneously remarked upon the removal of their "voices", and the fervour with which many of them held on to their delusional ideas was greatly reduced. In contrast, many of the control group appeared to regress and began to reveal more florid symptoms than they had shown for some years. This was probably due to the fact that many of the patients in both groups had in the past, been prescribed "chlorpromazine" drugs, which had been withdrawn a month before these trials commenced. By the end of the trial, many of the control group had been at least thirteen weeks without medication other than placebo.

Finally, there was a significant improvement in the amount and quality of useful activity demonstrated by the treated group. Patients who had previously been hostile and unco-operative on the wards became more useful group members. Several of the treated group succeeded in obtaining useful work around the hospital where before they had spent most of their time sitting in the wards preoccupied by their delusional ideas.

The results of the Mill Hill Vocabulary Tests were apparently contradictory. The improvement in score on the Synonyms test was significantly greater (at the 1 per cent. level) for the treated group, than for the untreated. In contrast, there was a significant drop in score (at the 5 per cent. level) for the treated group on the Definitions test. This apparent contradiction can perhaps be accounted for by the unsuitability of this latter test for assessing any improved clarity and efficiency of thought processes in schizophrenia. The more disturbed patients tended to attempt to answer more of the definitions than the less disturbed patients and many of these attempts were scoreable. When the clinical condition of these disturbed patients improved, they tended to attempt only those definitions for which they felt certain they knew the answer.

The sorting test results revealed that the treated group produced a significantly greater increase in the number of Acceptable sortings (5 per cent. level) following the trial. Because the number of Acceptable sortings possible was arbitrarily limited to ten, it was not considered strictly applicable to employ "t" tests for significance and an analysis was carried out using the square root transformation assuming the number of sortings might be distributed approximately as a Poisson variable (3, 4).

In contrast, there was not any significant reduction in the number of irrational sortings produced after treatment nor any speed up in average sorting time. If there was any effect, the treated group tended to be slightly slower at producing their sortings, although this was not statistically significant.

#### CLINICAL OBSERVATIONS

During the course of the trial, fairly close nursing observations were carried out on all the patients. No reports of any gross side-effects were made during the trial. At the close of the trial, several of the nursing staff stated that they believed they could distinguish those patients belonging to the drug group. This was largely because of the general improvement in the behaviour of these patients on the ward. Two patients developed mild extra-pyramidal symptoms, slight muscular rigidity, tremor, and increased salivation. None of these symptoms were obvious to the casual observer, and were only noticed by those members of the nursing staff with close continual contact with the patients.

## DISCUSSION

Twenty (eighteen) schizophrenic patients of relatively long standing were divided into two equal matched groups, each patient in one group had a partner in the other group. A "double-blind" trial was carried out over a period of sixty-two days using Vespral and a placebo. Marked improvement was observed in the treated group over the course of the trial. The florid psychotic syndrome was greatly reduced and the treated patients were better able to employ themselves usefully in the hospital. One patient of this group, who had previously been very disturbed, was able to leave the hospital, wherein he had been a patient for over eighteen years.

In contrast, the results of the psychological tests did not reveal such a consistent improvement in the thought processes of the treated group. There was some change, however, and this was on balance for the better. It would seem that following a course of treatment with this new ataractic, clear-cut social and general behavioural improvement was obtained, though the primary disorder of thought was little affected.

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# A SHORT SCALE FOR RATING PARANOID SCHIZOPHRENIA

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EXPERIMENTAL studies by O'Connor (2) and O'Connor and Rawnsley (3) have indicated the value of separating chronic schizophrenics into those who exhibit and those who do not exhibit paranoid symptoms. Other work by O'Connor and Venables (4) and Venables and O'Connor (6) has shown that performance of schizophrenic patients on experimental laboratory tasks may be clarified by dividing them into active or withdrawn groups by means of a rating scale (Venables, 5) in addition to a division on the basis of the presence of paranoid symptoms.

The aim of the present study is to devise a rating scale to give an operational definition of paranoid schizophrenia and to determine the relationship of this dimension to that defined by the "Activity-Withdrawal" scale.

The relevant literature was examined and colleagues' opinions requested on features which might be thought to characterize and conversely to be regularly absent in paranoid schizophrenia. Ten items which defined these features were extracted from the M.S.R.P.P. Scale (Lorr *et al.*, 1). Items 2, 4, 6, and 8 rated presence of delusions of external control, reference, persecution and grandeur, and 10 overtly expressed hostility. These symptoms were considered to be characteristic of paranoid schizophrenia. The remaining five, rating dirty unkempt appearance, incongruity of affect, disorientation in space and in time, and exhibition of bizarre postures were considered not to be characteristic of paranoid schizophrenia. All items were modified to be scored on a five-point basis if they were not already so scored. The ten items are shown in the Appendix.

One hundred male chronic ( $>$  two years stay) schizophrenic patients, mean age 43.20 S.D. 7.93 years, who had been in hospital for 14.18 S.D. 7.96 years were drawn at random from the total chronic schizophrenic population of a hospital. Only those patients who had undergone leucotomy were excluded. These 100 patients were rated on the ten selected items by seven charge nurses currently in charge of their wards. Scores on the ten scale items were intercorrelated and a centroid factor analysis carried out. Two significant factors and one of borderline significance were extracted. Loadings of the items on Factors I and II after a  $45^\circ$  rotation are shown in Table I (Column A). Factor II is clearly interpretable as paranoid schizophrenia. Items having high loadings on the first factor, orthogonal to Factor II, can be thought of as exemplifying deterioration or withdrawal.



TABLE I  
Factor Loadings on Rating Scale Items

|     | Factor I |      |     | Factor II |      | Factor III |      | Direction of Scoring       |
|-----|----------|------|-----|-----------|------|------------|------|----------------------------|
|     | A        | B    | C   | A         | B    | B          | C†   |                            |
| 1   | .72      | .65  |     | -.01      | -.13 | .13        |      | Dirty, unkempt             |
| 2   | -.08     | -.07 |     | .83       | .84  | .17        |      | Delusions of control       |
| 3   | .53      | .52  |     | .17       | .53  | .03        |      | Incongruity of affect      |
| 4   | -.09     | -.04 |     | .78       | .93  | -.08       |      | Delusions of reference     |
| 5   | .85      | .66  |     | -.20      | .15  | .14        |      | Disorientated for place    |
| 6   | .09      | .02  |     | .98       | .98  | .19        |      | Delusions of persecution   |
| 7   | .81      | .51  |     | .37       | .19  | .16        |      | Maintains bizarre postures |
| 8   | -.01     | -.25 |     | .82       | .51  | -.47       |      | Delusions of grandeur      |
| 9   | .94      | .67  |     | -.18      | .02  | .60        |      | Disorientated for time     |
| 10  | .16      | .13  |     | .46       | .25  | .36        |      | Hostile                    |
| 11* |          | .68  | .42 |           | -.04 | -.49       | -.54 | Motionless                 |
| 12  |          | .79  | .90 |           | -.37 | -.21       | .06  | Mute                       |
| 13  |          | .69  | .56 |           | -.22 | -.55       | -.70 | Appears tired              |
| 14  |          | .88  | .80 |           | -.22 | .26        | .19  | No friends                 |
| 15  |          | .66  | .90 |           | -.16 | -.33       | -.12 | Inaudible speech           |
| 16  |          | .89  | .76 |           | .08  | .10        | .14  | No interests               |
| 17  |          | .88  | .91 |           | -.13 | .06        | .03  | No conversation            |
| 18  |          | .68  | .48 |           | -.13 | -.52       | -.66 | Slow actions               |
| 19  |          | .83  | .89 |           | -.18 | .18        | .11  | Avoids others              |
| 20  |          | .90  | .91 |           | -.11 | -.15       | -.02 | Does not answer            |

\* Items numbered 11–20 are those numbered 1–10 in Venables (5) the direction of scoring being reversed.

† Factor II in Venables (5) scored in the reversed direction.

In view of the possible identification of Factor I with withdrawal a second set of scores for another 100 male chronic schizophrenics was collected on both the present ten items and the ten items from the "Activity-Withdrawal" scale (Venables, 5). This second group of patients whose mean age was 42.01 S.D. 8.62 years and who had been in hospital a mean length of time of 12.34 S.D. 8.73 years were randomly selected from the total chronic schizophrenic populations of two hospitals. Ratings on the total of twenty items were carried out by 14 charge nurses.

After intercorrelation of scores on the twenty items a centroid factor analysis was carried out. Three significant factors were extracted. Loading on Factors I and II rotated (17° 45' clockwise) and Factor III unrotated are shown in Table I (Columns B). Also in Table I (Columns C) are shown the loading previously obtained on Factors I and II (reversed) in the activity-withdrawal study. From these results it is seen that in the second analysis the loadings of the first ten items on the first two factors are in general similar to those obtained in the first analysis. Secondly, items 11–20 (items 1–10 in the activity-withdrawal scale) have high loadings on the first factor, previously defined in the first analysis by items 1, 3, 5, 7 and 9. It thus appears that Factor I can be considered as a factor similar to Activity-Withdrawal previously found, and that it is possible that withdrawal can also be considered as closely associated with deterioration. Thirdly, Factor III is seen to be loaded on the same items (11, 13 and 18) which previously had high loadings on Factor II in the Activity-Withdrawal analysis. These items are all concerned with motor inactivity in contrast to items not loaded on Factor III which are concerned more with social withdrawal. However, as in a social setting motor inactivity tends to bring about lack of social contact, the loadings of these items on the first factor are understandable. More difficulty is experienced in the interpretation of the high loading on Factor III of items 8 and 9. As argued previously (Venables, 5), there may not be much practical value in separating items having

loadings on Factor III from the rest of the items which have loadings on Factor I in view of their high correlation. However, it may be useful in future work to attempt to get a purer measure of Factor III. The inter-rater reliability was found to be .88 for scores defining Factor I and .78 for those defining Factor II. The correlation of Factor I with age is  $-.04$ , and of Factor II with age  $-.11$ . In no cases were any of the patients under dosages of drugs which might be expected to produce confusional symptoms.

In summary the study has produced a scale of four items, numbers 2, 4, 6 and 8, which effectively identifies patients who currently exhibit paranoid symptoms, item 10 probably not being sufficiently highly loaded on Factor II to be worth including. Social withdrawal can be defined with some purity by items 1, 5, 16, 17, 19 and 20. For future study items 9, 11, 13 and 18 partially define a factor of motor withdrawal or inactivity.

The lack of association between the factors "Paranoid-nonparanoid" and "Active-withdrawn" indicated by their orthogonality is reinforced by examination of the distribution of patients scored on these dimensions. Contrary to what might be expected clinically an insignificant chi-squared test of the distribution shows that there is no tendency for withdrawn-nonparanoids or active-paranoids to be more numerous when compared with the other two possible categories.

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#### APPENDIX

##### Items 1 to 10

For Items 11 to 20 refer to Venables (5)

1. Does he typically keep himself clean or must he be reminded to wash or be washed? Does he keep himself neat and his hair combed, or, are his clothes unbuttoned, disarranged, or soiled with food, dirt or faeces?

| 1                            | 2                         | 3                                      | 4                           | 5                                             |
|------------------------------|---------------------------|----------------------------------------|-----------------------------|-----------------------------------------------|
| Neater and cleaner than most | As neat and clean as most | Below average cleanliness and neatness | Distinctly sloppy and dirty | Requires special handling. Wets or soils self |

2. Does he tend to suspect or to believe on slight evidence or without good reason that people and external forces are trying to or now do influence his behaviour and control his thinking?

| 1                         | 2                                 | 3                       | 4                                              | 5                                                       |
|---------------------------|-----------------------------------|-------------------------|------------------------------------------------|---------------------------------------------------------|
| No unjustified suspicions | Will admit suspicion when pressed | Easily admits suspicion | Openly states others are trying to control him | Has firm conviction that he is influenced or controlled |

3. How incongruous are his emotional responses? E.g. giggling or crying for no apparent reason or not showing any emotion when emotion would be appropriately shown.

| 1         | 2                              | 3                              | 4                      | 5                         |
|-----------|--------------------------------|--------------------------------|------------------------|---------------------------|
| As normal | Slightly different from normal | Responses somewhat incongruous | Distinctly incongruous | Very markedly incongruous |

4. Does he tend to suspect or to believe on slight evidence or without good reason that some people talk about, refer to, or watch him?

| 1                         | 2                    | 3                       | 4                                | 5                                    |
|---------------------------|----------------------|-------------------------|----------------------------------|--------------------------------------|
| No unjustified suspicions | Will admit suspicion | Easily admits suspicion | Openly states that he is watched | Has firm conviction of being watched |

5. How well oriented is he as to where he is? Does he know (a) that he is in a hospital; (b) where the hospital is; (c) the name of the hospital?

| 1         | 2                      | 3                | 4            | 5                   |
|-----------|------------------------|------------------|--------------|---------------------|
| As normal | Sometimes makes errors | Slight confusion | Very muddled | Completely confused |

6. Does he tend to suspect or to believe on slight evidence or without good reason that some people are against him (persecuting, conspiring, cheating, depriving, punishing) in various ways?

| 1                                   | 2                                                          | 3                              | 4                                           | 5                                            |
|-------------------------------------|------------------------------------------------------------|--------------------------------|---------------------------------------------|----------------------------------------------|
| No unjustified suspicions expressed | When pressed expresses belief that he is conspired against | Frequently inclined to suspect | Frank inclination to believe in persecution | Strongly expressed conviction of persecution |

7. Does he assume or maintain peculiar, unnatural or bizarre postures?

| 1    | 2                 | 3                 | 4          | 5            |
|------|-------------------|-------------------|------------|--------------|
| None | On rare occasions | For short periods | Frequently | All the time |

8. Does he have an exaggeratedly high opinion of himself or an unjustified belief or conviction of having unusual ability, knowledge, power, wealth or status?

| 1                                    | 2                                                | 3                                              | 4                                              | 5                                                                           |
|--------------------------------------|--------------------------------------------------|------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------|
| No expressed high opinion of himself | When pressed expresses a high opinion of himself | Frequently expresses a high opinion of himself | Open conviction of unusual power, wealth, etc. | Strongly expressed conviction of grandiose or fantastic power, wealth, etc. |

9. How well oriented is he as to time? For instance, does he know (a) the season; (b) the month; (c) the calendar year; (d) the day of the week; (e) how long he has been in hospital?

| 1         | 2                    | 3                | 4                  | 5                           |
|-----------|----------------------|------------------|--------------------|-----------------------------|
| As normal | Occasional confusion | Slight confusion | Frequent confusion | Marked continuous confusion |

10. Compared to others how openly hostile is he? Does he show little hostility or a high degree of ill will, resentment, bitterness or hate?

| 1                 | 2                           | 3              | 4              | 5            |
|-------------------|-----------------------------|----------------|----------------|--------------|
| No open hostility | Relatively little hostility | Some hostility | Rather hostile | Very hostile |



# ANTICONVULSANTS AND MEGALOBLASTIC ANAEMIA

By

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THE development of megaloblastic anaemia as a complication of anti-convulsant therapy is now well recognized, and a total of thirty cases has been recorded.

Badenoch (1) reported the first detailed studies of megaloblastic anaemia developing in epileptic patients treated with phenobarbitone and epanutin, whilst Fuld and Moorhouse (6) reported the association with primidone (Mysoline) alone. In all the cases reported, the anaemia responded to folic acid therapy, whilst anticonvulsant drugs were continued.

Girdwood and Lenman (7) drew attention to the similar chemical structure of phenobarbitone, epanutin, primidone and folic acid. They suggested that the anticonvulsant, by acting as a competitive co-inhibitor in a tissue enzyme system involving folic acid, could produce a megaloblastic anaemia. This suggestion was, to some extent, confirmed by Chanarin, Elmes and Mollin (3), who demonstrated a normal clearance rate of intravenous folic acid in a patient with megaloblastic anaemia due to primidone. In other "folic acid deficiency" anaemias, due to pregnancy or intestinal malabsorption, the rate of clearance was increased because of depleted tissue stores of folic acid in these anaemias.

The elucidation of the mechanism by which the anaemias are produced, does not explain why only a small number of patients, treated with anticonvulsants, develop this complication. Individual factors, such as diet and duration of anticonvulsant therapy, may be important. Only full reporting of all cases with this complication will allow assessment of these factors.

Two further cases of megaloblastic anaemia due to anticonvulsants are reported.

*Case 1.* A 24-year old female epileptic presented in a psychiatric out-patient department, with symptoms of "anxiety" and progressive increase in frequency of epileptic seizures. Anti-convulsant therapy had consisted of phenobarbitone gr. 1 twice daily for six years, with the addition of primidone 750 mg. daily during the past 2½ years. The patient's diet had been conspicuously lacking in protein and fresh vegetables, because of her poor economic circumstances. She was admitted to a psychiatric unit in a general hospital for investigation.

Physical examination was normal apart from obvious anaemia. There were no haemorrhagic manifestations or abnormal neurological findings. Laboratory investigations: R.B.C. 1.9 million per cu.mm.; Hb. 8.5 g. per 100 ml.; M.C.V. 138 c.microns. Serum vitamin B12 was 160 µµg./per ml.; free acid was present on gastric analysis; fat balance and liver function tests were normal. Bone marrow puncture was megaloblastic.

Oral folic acid, 10 mg. twice daily, produced complete recovery from the anaemia. Six months later, the patient was in good physical health and there had been a marked reduction in the frequency of fits.

*Case 2.* A 45-year old, well-nourished, male, high-grade defective epileptic had lived in an epileptic hospital from 1934-55. He was then transferred to a mental hospital because of aggressive behaviour. Anticonvulsant therapy had consisted of phenobarbitone gr. iii. and phenytoin sodium gr. iii. daily for ten years, with the addition of primidone 250 mg. daily during the last three years.

A "pyrexia of unknown origin" of T.102° F. first drew attention to the haematological abnormalities. The patient was obviously anaemic, but made no complaints. Physical examination was normal with no neurological signs or haemorrhagic manifestations. Laboratory investigations: R.B.C. 1.4 million per cu.mm.; Hb. 36 per cent.; W.B.C. 2,300 per cu.mm. (46 per cent. polymorphs); M.C.V. 130 c.microns; P.C.V. 17 per cent. Bone marrow was megaloblastic. Liver function and fat balance tests were normal. Chest X-ray and urine examinations revealed no abnormality. Repeated attempts to perform a F.G.A. failed owing to the disturbed mental state of the patient. Tubeless gastric analysis was performed with the quinium resin test (Denborough, Retief and Witts (5)). This revealed the presence of free hydrochloric acid in the stomach.

Treatment consisted of oral folic acid 10 mg. b.d. this produced a 16 per cent. reticulocyte response on the sixth day.

There had been a progressive clinical improvement in the patient's haematological condition. Six months after the commencement of folic acid treatment, the blood count showed R.B.C.s 5.3 million per cu.mm.; W.B.C.s 7,000 per cu.mm.; Hb. 100 per cent. Anti-convulsant therapy has been continued throughout at the same dosage.

### DISCUSSION

Increase in frequency of epileptic seizures was observed in both the above cases. Failure to recognize the anaemia could lead to further increases in dosage of anticonvulsant drugs in an attempt to control the epileptic seizures, and it is possible that this, in turn, would further increase the severity of the anaemia. Deaths directly related to megaloblastic anaemias due to anticonvulsant drugs have been reported by Benians and Hunter (2) and Kidd and Mollin (8).

Haemoglobin estimations were carried out on a further fifty epileptics in mental hospital, who had been treated with anticonvulsants for from three to twenty years. No other significant anaemias were discovered. An annual haemoglobin estimation is a simple method of detecting this complication of anticonvulsant therapy at an early stage.

A review of all reported cases of this type of anaemia reveals that where primidone has been incriminated the average duration of therapy has been one and a half years, whereas with phenytoin sodium this has been five years. This discrepancy could be explained by the closer structural similarity of primidone to folic acid (Dawson and Johnson (4)).

"Tubeless gastric analysis", using the quinium resin test (Denborough, Retief and Witts (5)), is a reliable method of demonstrating free acid in gastric contents. It cannot give quantitative estimates of gastric acidity, but it is useful for the detection of achlorhydria in such conditions as pernicious anaemia and gastric carcinoma. In disturbed and unco-operative patients in mental hospitals, the estimation of gastric acidity by the "tube" method may frequently be impossible. Where this investigation is of importance, the method of "tubeless gastric analysis" forms a useful alternative, requiring only the giving of resin by mouth and the collection of urine specimens.

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# CHANGES IN CATECHOL AMINE RESPONSE TO SUCCESSIVE ELECTRIC CONVULSIVE TREATMENTS\*

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CHANGES in sympathetic nervous system responses have been noted to accompany changes in psychological states during psychiatric treatment. Funkenstein, Greenblatt and Solomon, observing the blood pressure response to epinephrine and methacholine, have reported a change in blood pressure patterns on the part of patients who benefited from electric shock treatment (1). Gellhorn has presented evidence that improvement in the psychoses is associated with heightened sympathetic reactivity (2).

Weil-Malherbe and Bone in 1953 introduced a method for the chemical determination of plasma epinephrine and norepinephrine (3), and Weil-Malherbe reported elevations of the plasma levels of both substances immedi-

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ately after electric shock treatment (4). He also reported on the effects of barbiturates and muscle relaxants in altering the catechol amine response.

In the present study, plasma catechol amine responses to electrically induced convulsions have been investigated in psychotic patients receiving electric shock treatment. We have determined catechol amine levels before treatment, changes of level after treatment, and the effect of successive seizures on the amount of amine response. We have also investigated the effect of the drugs used to modify shock treatment on the response, and the relationships between epinephrine and norepinephrine concentrations and various clinical and emotional states.

### SUBJECTS AND METHODS

The subjects of this study were twenty-five in-patients of the Massachusetts Mental Health Center (Boston Psychopathic Hospital), receiving electric shock treatment. Eleven were schizophrenic and fourteen had affective disorders. Patients were treated in the morning, two or three times a week, before breakfast, after sitting fifteen to twenty minutes in the waiting room. The first specimen of venous blood was drawn with the patient lying on a stretcher awaiting application of the treatment electrodes, and the second specimen approximately one minute after the start of electrical stimulation, at the time convulsive movements had largely disappeared. (In a previous study, it was found that peak epinephrine concentrations were recorded at one minute and peak norepinephrine concentrations between two and three minutes after the start of electrical stimulation.) The blood specimens were placed in tubes containing heparin and immediately centrifuged, the plasma then being drawn off and frozen.

With the unmodified form of treatment the only pre-medication was 1·3 mg. of atropine subcutaneously one-half hour before the seizure; no oxygen was given and some degree of cyanosis was usually present after unmodified treatments. With the modified form of shock treatment, atropine was also given one-half hour before the induced convulsion and ·2 to ·4 g. of thiopental sodium (pentothal sodium) and 20 to 50 mg. of succinylcholine chloride administered intravenously just before the convulsion. Thiopental was given to reduce anxiety and succinylcholine to soften the muscular seizure. Oxygen was given by bag pressure just before and after treatment. Fifteen subjects (9 with schizophrenia and 6 with affective disorders) received unmodified treatments and specimens were drawn before and after eighty-five seizures. The remaining ten subjects were given modified treatments and catechol amine levels were determined for seventeen seizures.

The average age of the unmodified group was 40 years and of the modified group 44 years. (The physical condition of both groups was similar, except that four of the ten patients receiving modified treatments had spinal abnormalities on X-ray, such as loss of a disc space or degenerative disc disease.)

With both forms of treatment the convulsive stimulus was given by a Reiter Electrostimulator Model No. RC47c. Subjects received full amperage for five to fifteen seconds, until a tonic state was achieved, and a much reduced amperage for the remaining thirty to forty seconds.

The amount of muscular movement during modified seizures was evaluated on a four-point scale. Zero meant no change from the usual unmodified seizure, 1+ indicated some arm and leg stiffness (during the tonic phase), 2+ arm stiffness but no leg stiffness, and 3+ both arms and legs relaxed and flaccid.

The diagnosis and psychological examination of each patient was recorded before the course of treatments. Changes in the psychological state were noted during the course of treatments and the patients were followed for a period of six months after convulsive therapy in order to determine whether re-hospitalization had taken place in this period.

The method used for the determination of catechol amine concentrations is a modification (5), similar to that described by Aronow and Howard (6), of the Weil-Malherbe and Bone technique (3). Values obtained for epinephrine and norepinephrine by this technique probably include undetermined amounts of other substances as well (7).

In the statistical analysis of the data non-parametric techniques were employed to avoid the assumption of normality of distribution of the material and because of the relatively small size of the samples. The Wilcoxon T test was used to determine the significance of any difference between the catechol amine levels before and after seizures; the Mann Whitney U test was used to test for significance between groups of subjects in terms either of the pre-treatment levels or the amounts of change after treatment. Determinations of the degree of relationship between two variables employed the Spearman Rank Order Correlation.

### OBSERVATIONS

Table I presents the mean plasma catechol amine levels before and after unmodified and modified electric shock treatments.

TABLE I

*Mean Plasma Catechol Amine Levels Before and After Unmodified and Modified Shock Treatments*

|                                        |    | Epinephrine<br>(micrograms/L.) | Norepinephrine<br>(micrograms/L.) | Number of<br>Deter-<br>minations |
|----------------------------------------|----|--------------------------------|-----------------------------------|----------------------------------|
|                                        |    | (s.d.)                         | (s.d.)                            |                                  |
| Normal resting levels (5)              | .. | .48 (.13)                      | 1.55 (.59)                        | 12                               |
| Unmodified convulsions:                |    |                                |                                   |                                  |
| Pre-convulsive level ..                | .. | .51 (.43)                      | 1.45 (.92)                        | 85                               |
| Post-convulsive level ..               | .. | 3.45 (.68)                     | 5.08 (1.86)                       | 85                               |
| Modified convulsions:                  |    |                                |                                   |                                  |
| Pre-convulsive level ..                | .. | 1.02 (.68)                     | 1.51 (1.13)                       | 13                               |
| Post-convulsive level ..               | .. | 1.18 (.79)                     | 1.65 (.86)                        | 13                               |
| Post-convulsive level ..               | .. | 2.28 (.23)                     | 1.73 (.40)                        | 4                                |
| (modification without 0 <sub>2</sub> ) |    |                                |                                   |                                  |

#### 1. Catechol Amine Levels Before Treatment

Psychotic patients awaiting unmodified treatment showed plasma catechol amine levels within normal limits for resting healthy subjects\*. The mean epinephrine value was .51 micrograms/L. and the mean norepinephrine value 1.45.

Table II demonstrates that the pre-seizure *epinephrine* levels rose in the course of successive treatments. Mean levels before the first seizure were significantly ( $P < .05$ ) lower than the levels before the fifth seizure or than the levels before the seventh, eighth, and ninth seizures ( $P < .02$ ). In contrast, there were no changes in the pre-seizure *norepinephrine* levels.

\* The mean resting levels for healthy young adults (tested at the conclusion of a basal metabolism test) are given in Table I. After activity the mean values are .51 micrograms/L. (s.d. .75) of epinephrine and 3.73 micrograms/L. (s.d. 1.35) of norepinephrine (5).

TABLE II

*Pre-seizure Plasma Epinephrine Levels and Rises in the Amount of Post-convulsive Response with Successive Seizures*

|                                       | Pre-treatment<br>Epinephrine Levels<br>(micrograms/L.) | Amount of Rise in<br>Epinephrine Levels<br>Post-convulsively<br>(micrograms/L.) |
|---------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------|
| First convulsion . . . . .            | ·38                                                    | 2·56                                                                            |
| Fifth convulsion . . . . .            | ·54                                                    | 3·00                                                                            |
| Seventh, eighth and ninth convulsions | ·58                                                    | 3·42                                                                            |

Patients awaiting the modified treatments had higher mean epinephrine values (1·02 micrograms/L.) than did patients awaiting the unmodified treatments. With the modified treatment there was, as with the unmodified, a tendency for the pre-seizure epinephrine levels to increase with successive treatments (up to the seventh), though the amount of data available is too small for statistical comparison. The pre-seizure norepinephrine level of the modified group (1·51 micrograms/L.) was not significantly different from that of the unmodified group.

## 2. Post-Convulsive Catechol Amine Levels

Significant elevations of the plasma catechol amine levels were noted in the blood specimens drawn after unmodified electric shock treatment. In the eighty-five experiments there was only one instance of failure to record a rise in epinephrine and norepinephrine levels.

There was a significant increase in the amount of epinephrine rise with successive seizures. Table II shows the mean rise following the first, fifth, and seventh, eighth and ninth treatments. (Between the first and fifth  $P < .05$ ; between the first and seventh, eighth and ninth  $P < .01$ .) There was also, as mentioned, an increase in the pre-seizure level of epinephrine with successive seizures.

In the course of successive treatments there was no significant change in the amount of norepinephrine response. The blood specimens were, however, drawn before the known peak of norepinephrine response.

Values were determined for the twenty-fifth treatment in one patient and there was still a significant post-convulsive elevation of both epinephrine and norepinephrine levels.

No correlation existed between the ages of the subjects and the epinephrine or norepinephrine response.

## 3. Correlation of Catechol Amine Response with Diagnosis, Psychopathology, and Outcome of Treatment

The fifteen patients who received modified treatments and on whom the catechol amine responses associated with four or more seizures were determined were first grouped according to diagnosis (whether schizophrenic or affective disorder), then according to presence of paranoid or depressive trends, and finally as to outcome at six months (whether in the community or hospitalized). There were no significant differences between any of the groups in either the mean pre-treatment values or in the response for either of the catechol amines.

The gradual increase in epinephrine levels and responses with successive seizures tended to correspond with the improvement in patients' clinical states, which was usually gradual. There were instances, however, in which clinical



improvement preceded or followed the increase of epinephrine values. Depressed patients, who showed the most improvement both during treatment and six months after, also showed the largest increases in pre-seizure epinephrine levels and post-convulsive responses, although the numbers are too small for statistical comparison.

#### 4. *Effects of Thiopental Sodium and Succinylcholine Chloride on Amine Responses*

The epinephrine response was significantly related to the amount of thiopental administered ( $P < .05$ ). The larger the dose of thiopental pre-medication the smaller the rise (or greater the drop) of epinephrine post-convulsively. This is shown graphically in Figure 1. There was no significant

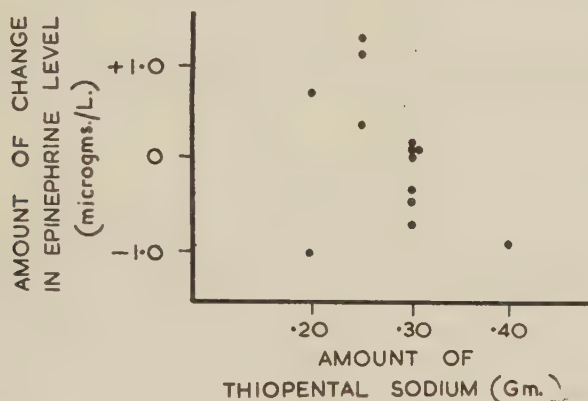


FIG. 1.—Relationship of thiopental dose and amount of change in epinephrine level.

relationship between the norepinephrine response and the amount of thiopental administered.

The norepinephrine response was related to the amount of muscular movement during the convulsion ( $P < .01$ ). The more complete the modification of the muscular seizure by the succinylcholine chloride, that is the less the muscular movements, the smaller the rise (or greater the drop) of norepinephrine as determined post-convulsively. Figure 2 graphs the amount of change in norepinephrine against the amount of modification.

The epinephrine response to shock treatment was not related to the amount of muscular movement during the seizure.

#### 5. *Effect of Anoxia on Amine Responses*

In an effort to determine the effects of anoxia on the plasma catechol amine response to shock treatment, four modified seizures were given without oxygenating the patients before or after treatment. Table I presents the mean epinephrine and norepinephrine levels following these four modified treatments without oxygen. The post-convulsive level of epinephrine was significantly higher than was the epinephrine level of patients pre-medicated with comparable amounts of thiopental and succinylcholine and given oxygen ( $P < .01$ ). The norepinephrine level was, however, not significantly higher. The post-convulsive

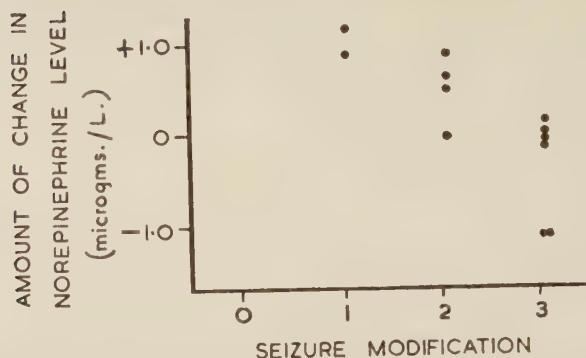


FIG. 2.—Relationship of degree of seizure modification and change in norepinephrine level.

levels of both epinephrine and norepinephrine in patients modified but not given oxygen were lower than the post-convulsive levels of the patients given unmodified seizures ( $P < .01$ ).

### DISCUSSION

The mean catechol amine levels of our psychotic subjects awaiting unmodified shock treatment were within the normal limits for healthy young adults not under stress. Pre-treatment epinephrine concentrations, however, tended to be below the norm early in the course of treatments and to rise above it for the later seizures (see Table II). The amount of epinephrine response to individual seizures also increased with successive treatments.

The findings of an increased pre-treatment epinephrine concentration and an increased epinephrine response with successive treatments support the hypothesis that heightened sympathetic reactivity develops in the course of electric shock treatment. Indirect support of this hypothesis has been provided by the work of Solomon *et al.* (8) on galvanic skin responses and that of Gellhorn and Safford (9) on blood sugar patterns. In addition, Funkenstein, Greenblatt and Solomon have reported a decrease in the hypotensive effect of methacholine and an increased reaction to intravenous epinephrine after successful courses of electric shock treatment, which they explained as the result of heightened sympathetic reactivity to stimulation (1). They also noted a decreased basal blood pressure after successful treatment, which suggested to them a lowered "basal sympathetic tension". The patients in the present study were not tested in a basal state and their rising pre-seizure epinephrine levels may reflect changes in response to the stress of awaiting shock treatment as much as they do changes in "basal sympathetic tension".\*

Rising pre-treatment epinephrine levels may suggest an increase of anticipatory anxiety with successive seizures. This explanation of the changes noted in pre-treatment epinephrine levels cannot be fully excluded, but it has not been supported by observations of patients awaiting shock treatment (11). In general, apparent anxiety decreased in the course of treatments.

Michael found the lymphocytic reaction to electric convulsions similar to that of injected epinephrine (12) and Michael and Brown have reported a

\* Wenger, Engel and Clemens have recently stressed the importance of separating measures of autonomic balance in a resting state from measures of response patterns to stimuli (10).

decrease in the amount of lymphocytic rise with successive seizures (13). Altschule, Parkhurst and Tillotson made a similar observation on the eosinophilic response to shock treatment; they found that the usual post-seizure fall in eosinophils tended to decrease if treatments were given every five days or more often (14). One explanation of these results would be a fall in adrenal gland responsiveness with successive seizures. It may be, however, that these studies imply a decrease in the ability of certain systems, such as those which control the lymphocytic and eosinophilic levels, to respond to adrenal hormones or to other stimulating effects of the seizures.

The finding reported here, of an increased or continued adrenal responsiveness over the courses of treatment studies, is in keeping with the work of Holland and Schumann (15) and Zileli *et al.* (16); they noted a rapid re-synthesis of catechol amines in the adrenal medulla after various experimental procedures.

It is not obvious why the epinephrine levels before modified shock treatment should be above those before unmodified treatments. In another study (11), comparing the reactions of patients to modified and unmodified seizures, it was found that patients given modified treatments because of advanced age or physical disabilities expressed greater fear of treatment and were more resistant to accepting it than patients awaiting unmodified seizures. It is therefore possible that the higher pre-treatment epinephrine levels of the modified group in the present study (slightly older and with more physical disabilities than the unmodified group) partly reflect a greater fear of treatment than that experienced by the unmodified group.

The post-convulsive levels found in this study were higher than those Weil-Malherbe has reported (4). This discrepancy may be the result of differences in chemical technique, type of shock-induction, severity of seizures, timing of samples, the degree of hypoxia, or other factors. The possible importance of hypoxia is underlined by some of the present data: when modified patients were not oxygenated before and after treatment there was a greater catechol amine response than when oxygen was given. Satake has also reported that asphyxia is a powerful stimulant to epinephrine secretion (17). These considerations emphasize the danger of assuming that any effects of electric shock treatment (including those chemical effects studied here) are directly the result of electrical stimulation and not secondary to phenomena accompanying the seizure.

Elmadjian and Hope have reported a relationship between aggressive-hostile-active emotional display and the excretion of norepinephrine (18). In the present study a relationship between the amount of muscular movement during a fit and the norepinephrine concentration after it was noted. Convulsions in which there was little modification or reduction of muscular movement were generally followed by large increases of norepinephrine. These results suggest that the patterns of norepinephrine excretion Elmadjian and Hope describe may be a result as much of the muscular activities of the subjects as of their specific emotional states. In the healthy young adults tested to determine the normal values of the chemical method employed for the present study, activity affected the epinephrine values very little, but it produced significant changes in the norepinephrine levels (5). These results are, however, to be contrasted with those of Von Euler and Hellner, who found that physical exercise in healthy subjects produced approximately equal elevations of the urinary excretions of both epinephrine and norepinephrine (19). The differences observed in the present study from those of Von Euler and Hellner may reflect differences in the amount of exercise employed in the two sets of experiments. The subjects of the Von Euler experiments underwent very heavy exercise, as only under



these conditions were the responses of the adrenergic system found to be large enough to show in the urine. It is possible that during very heavy exercise, other factors, such as anxiety, may increase the epinephrine response. It is also possible that the differences in the findings of the two sets of experiments are the result of difficulties in comparing plasma and urinary levels. It is not known, for example, whether the rate of removal of catechol amines from the plasma is the same under the various experimental conditions.

Thesleff has reported that succinylcholine in large doses affects transmission at autonomic ganglia (20). This raises the possibility that the relationship noted here between the norepinephrine response and the degree of effectiveness of succinylcholine in modifying seizures may be a result of direct autonomic effects of succinylcholine. The amounts of succinylcholine required to produce any measurable changes in transmission at autonomic ganglia are, however, many times the amounts used in the present study.

Weil-Malherbe reported that the epinephrine response to electric shock treatment was little changed by the administration of a barbiturate before the seizure (4). In the present study it appeared that the epinephrine response could be reduced or reversed if enough barbiturate were given. Weil-Malherbe also suggested that the production of epinephrine was related to the clinical effectiveness of shock treatment (4). In a separate study, using amounts of barbiturate and succinylcholine which reduce the plasma catechol amine response to seizures, no differences in the clinical outcome of treatment compared with the results of unmodified seizures were observed (11). These data suggest that the production of plasma catechol amines is not an important part of the mode of clinical action of electric shock treatment, although the creation of a state of heightened sympathetic reactivity may be.

#### SUMMARY

Plasma catechol amine concentrations were determined before and after one hundred and two electric convulsive treatments of twenty-five psychotic patients. The epinephrine and norepinephrine levels of patients awaiting unmodified seizures were within the normal limits for healthy subjects not under stress. Pre-treatment epinephrine levels tended to be below the normal average early in the course of treatments and to rise above it with later seizures.

Significant elevations of both epinephrine and norepinephrine consistently followed unmodified shock treatments. The amount of epinephrine response increased with successive seizures up to the ninth. After as many as twenty-five treatments significant post-convulsive elevations of both amines were still found.

Use of the seizure-modifying agents thiopental sodium and succinylcholine chloride significantly reduced the catechol amine response to shock treatment. The epinephrine response was related to the amount of thiopental administered and the norepinephrine response to the amount of muscular movement during the seizure.

The finding of an increase of pre-treatment levels and post-convulsive elevations of epinephrine with successive seizures gives direct support to the hypothesis that electric shock treatment produces heightened sympathetic reactivity. It cannot be concluded, however, that the production of plasma catechol amines is necessary to the clinical action of electric shock treatment, as the results of shock treatment are not changed by agents, such as thiopental and succinylcholine, which decrease the catechol amine response.

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# A CASE OF PHOCOMELIA ASSOCIATED WITH SEVERE MENTAL DEFICIENCY

By

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PHOCOMELIA is a congenital malformation of the osseous system characterized by the absence or extreme smallness of the arms, forearms, thighs and legs, producing a pronounced shortening of limbs. The hands and feet, which may be fairly normal in appearance and development, seem inserted more or less directly into the shoulders or pelvis of the patient. As the micromelic appendages resemble the physical outlines of a seal's flippers, the condition is known as phocomelia.\*

Sometimes, however, only the arms or the legs are affected and less uncommonly, a single arm or leg with all the other limbs otherwise normally formed. The hands and feet, however, may show numerous congenital anomalies such as disproportionately short, long, supernumerary and webbed fingers or toes.

This exceedingly rare bone anomaly is related to pre-natal factors arising during the early phase of foetal development which prevent the laying down of certain parts of the osseous system. The cranial vault, the vertebral arches, the pelvic and the shoulder girdles, may likewise manifest serious structural deficiencies.

Short references to phocomelia have been made by Church (1911), Aschoff (1928) and Kaufmann (1929) but the most descriptive record with photographs has been contributed by Patten (1946). None of the above-mentioned authors, however, have investigated psychologically the mental condition and intellectual state of their patients.

A case of phocomelia has recently been admitted to this Mental Deficiency Institution. She is a white baby girl aged 3·7 years chronologically, having a mental age of 8·2 months and an intelligence quotient of 19 being classified as belonging to a low-grade type of mental defect (Idiot).

She is of Caucasian race, and comes from a non-farm, rural environment. She is the last born of two siblings, her older brother being of normal physique, intelligence and in good health.

The mother, who is a diabetic with a history of psychosis, was 35 years old and the father, who has a peptic ulcer, 43 at the birth of the patient. Histories of alcoholism in the paternal, and psychosis in the maternal grandparents have also been recorded.

## PERSONAL HISTORY

The patient was born at eight months. The mother felt well during the pregnancy, and labour was stated as having been uneventful. The baby weighed 5 pounds at birth and had feet and a left arm growing out of the

\* Phocos, Greek for seal; melos, Greek for limb.





A case of Phocomelia Associated with Idiocy.

lower torso and left upper shoulder-chest region, respectively. She had a hare lip and a cleft palate which were recently repaired surgically. Otherwise she was a healthy baby, breathing without difficulty, and moving about in the crib playfully. No other information is available.

#### *Physical Examination*

Skin: Clear.

Scalp: Normal.

Hair: Fair and fine.

Eyes: Blue; palpebral fissures are narrow, with a certain degree of slanting towards the outer angles.

Nose, lips and palate plastically repaired.

Lungs: Clear to A. and P.

Heart: No murmurs heard and cardiac outlines normal.

Neuro-muscular system: She is right-handed with pareses of both lower extremities and left upper limb. The grip of the right hand is normal, reflexes of left biceps active, right triceps sluggish. Left biceps and triceps reflexes are absent. The upper and lower abdominal reflexes, both left and right, are active, and the plantar reflexes are normal bilaterally.

#### *Special Data*

Weight on admission: 14 lb. 6 oz. (Since her admission three weeks ago, she has gained over 1 lb. 4 oz. in weight.)

Length: 22 inches.

Cranial circumference:  $17\frac{1}{2}$  inches.

Length of normal right arm and forearm: 9 inches, shortened left arm and forearm 5 inches. The lower limbs measure only  $7\frac{1}{2}$  inches, including feet.

Torso-Leg Ratio: 19 inches/ $14\frac{1}{2}$  inches.

The inner aspect of the skin of the shortened arm is adherent along the axillary line to the skin of the outer chest wall; the left elbow joint is movable and the left forearm overly shortened.

Feet: There are syndactylies involving the second and third as well as the fourth and fifth toes of both feet, which are unusually small. A pilo-nidal sinus is seen in the ilio-coccygeal region.

*Roentgenological Report*

There are most amazing osseous defects in this child. The left humerus, radius and ulna are underdeveloped and deformed but the bony outlines of the right upper extremity are normal. Both femurs are hypoplastic and of abnormal shape and both tibiae and fibulae are absent. The facial bones, particularly the sphenoid, ethmoid, maxillary and mandibular structures, are rather smaller than usual, and there is a cleft in the bony palate. The left shoulder blade is hypoplastic, of irregular outline, showing some defect in its centre. The cranial vault exhibits slight digital markings with some thinning of inner table.

*Orthopaedic Consultation*

Congenital absence, multiple in extremity bones, left-upper and both lower limbs markedly shortened. Cleft palate, hare lip repaired. Later in childhood, if it appears indicated at that time, prosthetic considerations may be given.

*Ophthalmological Consultation*

OD Pup. 3<sup>5</sup> reg. and act. Homatropine instilles. Media clear. Discs clear, good colour. Vessels and maculae normal. OS similar to OD. EQM normal. No pathology seen.

*Psychological Consultation*

Gross motor patterns fall between the eight- and sixteen-week levels. Standing, unable to support any weight, below twelve weeks; supine, pulled to sitting, complete head lag twelve weeks; prone, head zone III 16-week level. Adaptive patterns are somewhat higher, i.e. radial palmar grasp 28 weeks, and transfers adeptly 28 weeks. No verbalization is elicited. Sphincter control is absent, cannot sit up or feed herself. Chronological age: Three years seven months; mental age, eight and two-tenths of a month, intelligence quotient 19. Classification: Idiocy.

## SUMMARY AND DIAGNOSIS

In view of the above findings, it appears that this child manifests the congenital malformation described as phocomelia which is complicated by a severe degree of intellectual defect (Idiocy), cleft palate, hare lip, skull anomalies, pedal syndactylism and pilo-nidal sinus.

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# CUTIS ANSERINA: ITS SIGNIFICANCE IN THE PROGNOSIS OF MENTAL ILLNESS\*

By

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THE autonomic nervous system activity that has been observed to accompany grand mal epilepsy does not occur consistently with the seizures produced by electric convulsive treatment. The dilated pupils, flushing, lacrimation and gooseflesh which appear during the tonic spasm of the electrically induced seizure, and which are the outward manifestations of the autonomic storm within, are often not readily observed because of their transience; they begin to fade almost as soon as they appear and may be gone with the onset of the clonic spasm. Different patients exhibit them in different degrees and the same individual may show changes in the amount of autonomic response over a course of treatments.

Studies of autonomic activity have suggested a relationship between subjects' physiological patterns and their psychological status and response to psychiatric treatment. Funkenstein, Greenblatt and Solomon, for example, observing the changes in blood pressure that followed injections of epinephrine and methacholine, have reported distinct patterns of blood pressure change on the part of patients who benefited from electric shock treatments (1). Gellhorn has presented evidence from blood sugar and other studies that improvement in psychoses is associated with an increased autonomic responsiveness (2).

The authors of the present paper were in search of a simple physical sign that might, like these laboratory procedures, reflect autonomic activity and be a convenient and reliable measure for clinical use. It had been observed that the gooseflesh response to electrically induced seizures varied greatly from patient to patient, some showing marked or moderate eruptions and others little or no discernible response. We were interested in whether this variation in gooseflesh was a result of variations in the method of administering

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the seizure or of some factor inherent in the subject, such as age, sex, diagnosis or prognosis. The discovery of significant correlations between the extent of gooseflesh response and diagnosis or prognosis might provide psychiatric practice with a useful clinical sign.

### SUBJECTS AND METHODS

The subjects were forty-three in-patients of the Massachusetts Mental Health Center (Boston Psychopathic Hospital) referred for electric convulsive treatment. Ten received diagnoses of schizophrenia, and thirty-three others diagnoses of affective disorder, including involutional depressions, psychotic and neurotic depressive reactions and manic-depressive psychoses of both manic and depressive type. All the diagnoses were made before treatment.

Observations were collected on twenty-six additional patients referred for shock treatment from the out-patient department. No follow-up data were gathered on this group, for only the relationship between gooseflesh response and age was studied.

Patients were treated in the morning, two or three times a week, before breakfast, after sitting fifteen to twenty minutes in the waiting room. All treatments were administered with the Reiter Electrostimulator Model RC 47c. Subjects received full amperage for ten to fifteen seconds, until a tonic state was reached, and a much reduced amperage for the remaining thirty to forty seconds.

All the patients were given .0009 Gm. atropine subcutaneously one-half hour before treatment and pentothal sodium (.2–.3 Gm.) and succinylcholine chloride (.025–.050 Gm.) intravenously immediately before applying the electric shock. The current was applied one minute following completion of the succinylcholine injection. Patients also received positive pressure oxygen during the periods of apnoea before and after treatment.

The extent of gooseflesh response was rated during the period of tonic and clonic movements. One observer made all the ratings and used as the test area the upper chest, bounded by the nipples and outer ends of the two clavicles. Gooseflesh was graded on a 3-point scale, none (0), moderate (1) and marked (2). The rating was based on the maximum gooseflesh response observed during the fit.

Immediately after the course of treatments, each patient's psychiatrist was asked to rate the degree of the patient's improvement, little or none, moderate, or marked. The above data were then correlated with status of patient two months after treatment, whether still hospitalized or discharged.

### RESULTS

Table I relates the mean gooseflesh responses for all subjects in the two diagnostic groups with status two months after the end of the treatment.

TABLE I

| Mean Responses of<br>Those Discharged<br>Within 2 Months<br>After Treatment |    |    |    | Mean Responses of<br>Those Not Discharged<br>2 Months After<br>Treatment |  |                   |  |
|-----------------------------------------------------------------------------|----|----|----|--------------------------------------------------------------------------|--|-------------------|--|
| All subjects                                                                | .. | .. | .. | 1.2 (30 subjects)                                                        |  | 1.1 (13 subjects) |  |
| Affective disorders                                                         | .. | .. | .. | 1.2 (25)                                                                 |  | 0.6 (8)           |  |
| Schizophrenic disorders                                                     | .. | .. | .. | 0.9 (5)                                                                  |  | 1.8 (5)           |  |

There is no statistically significant difference between the means of gooseflesh response when all the subjects' responses are averaged and the subjects divided into a favourable and unfavourable group as to outcome. When the subjects are separated by diagnosis, however, significant differences appear. It is apparent that among the patients with affective disorders those with the more favourable outcomes have larger mean gooseflesh responses ( $P$  less than  $\cdot 01$ ). The opposite is true of the schizophrenic subjects. With these patients, a favourable outcome is associated with relatively small gooseflesh responses ( $P$  less than  $\cdot 025$ ).

The subjects with the least favourable outcomes had the most extreme responses, in the case of the schizophrenic patients the greatest and in the case of the depressed the smallest.

Table II shows the relationship between the magnitude of gooseflesh response and improvement as rated just after each course of treatments. The trend of the results with the affective illnesses is similar to that of Table I, but the differences are not statistically significant.

TABLE II

|                         |    |    |    |    | Mean Responses of Those With<br>Improvement Rated as: |          |                   |
|-------------------------|----|----|----|----|-------------------------------------------------------|----------|-------------------|
|                         |    |    |    |    | Marked                                                | Moderate | Little or<br>None |
| Affective disorders     | .. | .. | .. | .. | 1.1                                                   | 1.0      | 0.8               |
| Schizophrenic disorders | .. | .. | .. | .. | 1.3                                                   | 1.8      | 1.5               |

Table III presents the data on a larger group of subjects (for some of whom no information on outcome was available), relating *age* and gooseflesh response.

TABLE III

| Age (by decades) |    |    |    |    | Mean Gooseflesh<br>Responses | Numbers of<br>Subjects |
|------------------|----|----|----|----|------------------------------|------------------------|
| 20-30 years      | .. | .. | .. | .. | 1.7                          | 7                      |
| 30-40 years      | .. | .. | .. | .. | 1.1                          | 8                      |
| 40-50 years      | .. | .. | .. | .. | 1.3                          | 12                     |
| 50-60 years      | .. | .. | .. | .. | 0.9                          | 16                     |
| 60-70 years      | .. | .. | .. | .. | 0.8                          | 20                     |
| 70-75 years      | .. | .. | .. | .. | 0.4                          | 6                      |

It is obvious that the magnitude of gooseflesh response, as measured in this study, falls with increasing age. Are the differences between the groups presented in Table I the result of difference in age? Table IV shows the mean ages of the affective and schizophrenic groups divided as to outcome at 2 months.

TABLE IV

|                         |    |    |    |    | Mean Age of Those<br>Discharged Within<br>2 Months<br>(years) | Mean Age of Those<br>Not Discharged<br>Within 2 Months<br>(years) |
|-------------------------|----|----|----|----|---------------------------------------------------------------|-------------------------------------------------------------------|
| Affective disorders     | .. | .. | .. | .. | 51.8                                                          | 50.1                                                              |
| Schizophrenic disorders | .. | .. | .. | .. | 43.8                                                          | 25.0                                                              |

The age difference in the affective disorders is not significant. The tendency of gooseflesh responses to fall with age (Table III) probably does not therefore explain the relationship between response and clinical outcome found for this group (Table I). The age difference in the schizophrenic group, however, is significant ( $P$  less than .01) and may influence the relationship for schizophrenic subjects in Table I. It is also interesting that with the latter group outcome appeared to improve with advancing age.

A relationship between the *sex* of patients and the amount of gooseflesh response is apparent from Table V.

TABLE V

|         |    |    |    |    |    |    |    |    | Mean Gooseflesh Response |
|---------|----|----|----|----|----|----|----|----|--------------------------|
| Males   | .. | .. | .. | .. | .. | .. | .. | .. | 1.4                      |
| Females | .. | .. | .. | .. | .. | .. | .. | .. | 0.7                      |

This highly significant relationship ( $P$  less than .001) is probably not a function of differences in the distribution of male and female patients among different age or diagnostic groups. No statistically significant correlations between the sex of the subjects and their age or diagnoses were found.

Is there a relationship between the sex of these patients and the outcome of treatment at two months? Can the differences noted in Table I be the result of differences in the distribution of the sexes among the groups? There are no significant differences in the numbers of men or women in the two outcome groups for the schizophrenic subjects but there are differences for the affective illnesses. The distribution of the sexes (of patients with affective illnesses) is shown in Table VI. These differences are significant at the .05 level.

TABLE VI

|         |    |    |    |    | Numbers Discharged Within 2 Months After Treatment | Numbers Not Discharged Within 2 Months |
|---------|----|----|----|----|----------------------------------------------------|----------------------------------------|
| Males   | .. | .. | .. | .. | 19                                                 | 3                                      |
| Females | .. | .. | .. | .. | 6                                                  | 5                                      |

It then becomes necessary to determine if the gooseflesh responses of the affectively ill men and women, averaged independently, are related to outcome. These determinations are shown in Table VII.

TABLE VII

|         |    |    |    |    | Mean Responses of Those Discharged Within 2 Months After Treatment | Mean Responses of Those Not Discharged |
|---------|----|----|----|----|--------------------------------------------------------------------|----------------------------------------|
| Males   | .. | .. | .. | .. | 1.42                                                               | 1.05                                   |
| Females | .. | .. | .. | .. | 0.6                                                                | 0.4                                    |

The relationship between gooseflesh response and outcome of treatment in the affective disorders (Table I) now appears partly the result of differences in the distribution of the sexes among the groups. However, where correction is made for the sex factor (Table VII), there are still variations in gooseflesh responses that are related to outcome, especially among the male subjects.

Are differences in the dose levels of the modifying agents pentothal sodium



and succinylcholine chloride related to the differences in gooseflesh responses? Table VIII compares the dose levels of the modifying drugs in affectively ill patients for the two outcome groups.

TABLE VIII

|         |    |    |     | Mean Modifying Doses<br>of Those Discharged<br>in 2 Months<br>(Gm.) |          | Mean Modifying Doses<br>of Those Not<br>Discharged<br>(Gm.) |          |
|---------|----|----|-----|---------------------------------------------------------------------|----------|-------------------------------------------------------------|----------|
|         |    |    |     | Pentothal                                                           | Succinyl | Pentothal                                                   | Succinyl |
| Males   | .. | .. | ..  | .26                                                                 | .032     | .26                                                         | .028     |
| Females | .. | .. | ..* | .22                                                                 | .032     | .23                                                         | .030     |

Only in the case of succinylcholine chloride are there differences in dosage and, contrary to expectation, the group of subjects evidencing the largest gooseflesh responses received the larger amounts of muscle relaxant.

There were no significant changes in the magnitude of gooseflesh response with successive treatments.

### DISCUSSION

Under natural conditions, gooseflesh or pilo-erection occurs in two circumstances: as the mechanism involved in conjunction with somatic and vascular musculature in the generation of heat, and as part of the visceral responses that we associate with emotion. The neo-cortical and rhinencephalic areas which subserve these activities discharge by way of connections to the hypothalamus and from the hypothalamus to the preganglionic centres of the brain stem and thoracolumbar cord. The impulses finally are transmitted to the erectores pilorum muscles themselves, in man slender bands of unstriped muscle connecting the root of the hair follicle below the subaceous gland to the epidermis.

The emotional significance of pilo-erection has been the common knowledge of poets and naturalists for centuries. The ghost of Hamlet's father had a tale he promised Hamlet would make:

"Thy knotted and combined locks to part,  
And each particular hair to stand on end,  
Like quills upon a fretful porpentine." (3)

Charles Darwin (4) had also observed the "fretful porpentine" and he described the erection of quills, spines and hairs in animals during states of emotional excitement. Interested in the appearance of gooseflesh in mental illness, he reported that bristling of the hair, "so common in the insane", is not always associated with terror, but most often seen in mania and melancholia. The report of a doctor's wife was cited; she predicted that a certain lady suffering from acute melancholia "will soon improve, for her hair is getting smooth; and I always notice that our patients get better whenever their hair ceases to be rough and unmanageable". With a man "now in the asylum", Darwin noted the observation that before the recurrence of each maniacal paroxysm "the hair rises up from his forehead like the mane of a Shetland pony". The appearance of vigorous autonomic activity in patients who recovered from such illnesses as mania and melancholia is in accord with our findings.

A decline in magnitude of gooseflesh responses with advancing age was another observation of the present study. The reasons for this are not clear. Blumberg, Cohen and Miller have reported that the extent of the hypotensive

response to methacoline in mental patients also changes with age, towards a pattern of the prognostically favourable type (5). This finding suggested that the favourable outcome of electric convulsive treatment with depressed patients was as much a function of their generally advanced age as it was of their having blood pressure responses of the favourable type. In contrast to this, the present study suggested that depressed patients who reacted favourably to electric convulsive treatments were those with larger gooseflesh responses, that is, responses more typical of younger subjects.

This was not the case with the schizophrenic subjects. The schizophrenic subjects who did well had smaller responses than those who did poorly. This difference between schizophrenic and depressed patients does not appear so striking, however, when it is noticed that it is *extreme* responses, great or small, that are associated with unfavourable outcomes. The schizophrenic subjects who showed the poorest results of treatment had the very greatest responses, as the depressed patients who did poorly had the very smallest. The subjects who did best, whether schizophrenic or depressed, had responses close to the mean of the entire group. It appears to be in this mean response range that electric convulsive treatment is most effective.

Males showed significantly more gooseflesh response than did females. The fact that more men responded favourably to treatment than did women is not the whole explanation, for when correction was made for the outcome of the treatment, there were still large differences in the magnitude of gooseflesh between the sexes. It may be that this is due to differences in the size or number of erector muscles in men and women.

Several investigators have presented evidence that the autonomic response to electric convulsive treatments increases with successive seizures. Gellhorn and Safford noted a change in blood-sugar reactions suggestive of increased autonomic activity with successive seizures (6), and Havens and associates have reported an increase in serum epinephrine response to shock treatment in the course of therapy (7). There was no evidence in the present study of any such change in autonomic responsiveness as reflected in the magnitude of observed gooseflesh.

The search for reliable physical and psychological signs in psychiatry has not generally been a fruitful one. The lack of adequate methods of measurement, great variations in the clinical material and the influence of the different situations in which observations are made have all worked to confound the investigator. The present study has not escaped these difficulties. The gooseflesh response is only roughly quantifiable and the method by which it has been elicited, electric convulsive treatment, is one of limited applicability. Certainly the finding reported here requires confirmation in additional subjects and with methods of eliciting the response safer and more convenient than the present method.

#### SUMMARY

In an effort to develop a prognostic sign useful to psychiatric practice, the gooseflesh response to electric convulsive treatment was observed in 43 hospitalized mental patients. The magnitude of the gooseflesh response was inversely related to the age of subjects and was greater in men than in women. Patients with affective illnesses evidenced a positive relationship between the magnitude of their gooseflesh responses and favourable outcomes of treatment.

#### ACKNOWLEDGMENTS

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# EMOTION AND BLOOD-PRESSURE

By

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THE general aim of the experiment was to discover whether, during an interview directed at discussing the patient's life, there was any significant alteration of blood-pressure, heart rate or brain waves in association with emotional content; as it turned out, changes in blood-pressure proved to be the most rewarding field for study and in consequence this aspect was accorded more attention.

Although some work has already been carried out in this field both in the United States and in this country (Gold, 1943; Hambling, 1952; Moses *et al.*, 1956; Palmer, 1950; Wolf *et al.*, 1948), it was thought that the techniques employed were not sufficiently rigorous to allow of any exact correlations being made between emotional states on the one hand and physical changes on the other. It has of course long been known that life situations and emotional states have some general bearing on physical changes, particularly in autonomic function, but it was felt that causal relationships had so far been only tenuously established mainly because a considerable interval of time usually elapses between the alleged causative emotional states and the consequent physical changes. Accordingly it was thought that a clearer idea of causal interrelationship between emotional and physical states could be gained by carrying out contemporaneous observations of both under special test conditions. It was also thought that any recording, either of emotional content or of physical changes, should be of a permanent nature and if possible susceptible to exact measurement.

This investigation, which was pursued fairly intensively over a period of two years, produced a great deal of data which will be reported elsewhere. However, for the purposes of the present paper, only the salient points have been noted and all tabular material has been omitted. Unless it is stated to the contrary, it may be taken that all findings are statistically significant, at the 0.05 level of confidence.

## TECHNIQUE

*The Interview.* All subjects were given straightforward "psychiatric" interviews of a biographical kind, that is to say, the following aspects were covered in all cases but in no standardized or rigid order—Present Health; Past Health; Personal History (including early childhood, schooling, occupation, marital, domestic and recreational life); Personality (including special interests, attitudes, ambitions, temperament), and Family History. All interviews, with the exception of those involved in the Special Investigation reported later, were conducted by the same physician (M.V.) according to this pattern.

The interviews varied in length but usually lasted 20-30 minutes; some interviews in which subjects seemed eager to discuss their problems at greater length lasted for up to one hour. The interview was conducted with the patient lying relaxed on a couch after a rest period of 10-15 minutes. Usually the interviewer did not enter the room, where the subject had been resting and attached to the apparatus, until the actual interview was about to begin.

The interview room was one of a suite of two rooms divided by a partition of "one-way" glass. The room itself had the appearance of a formal consulting-room, all recording apparatus being located in the adjoining room on the other side of the glass screen. The leads connecting the patient to the recording apparatus were channelled through the wall in as unobtrusive a manner as possible.

Most subjects were interviewed on one occasion only, but in five cases a series of interviews was conducted. One of those patients, who showed marked fluctuations in blood-pressure, was made the subject of a special investigation and interviewed on 24 occasions.

## RECORDING APPARATUS

*Sphygmomanometer.* The method adopted was an adaptation of the standard clinical procedure. A cuff round the patient's left arm was connected through the wall to a 7-inch (175 mm.) aneroid sphygmomanometer, and a large cylinder of compressed air operating through a reducing valve produced a smooth and rapid build-up of pressure in the cuff. The flow of air was cut off, and pressure reduced, by an orthodox needle valve. A flat stethoscope chest-piece made of "coldlite" was fixed over the brachial artery at the elbow by adhesive tape and held in place by an elastic cotton bandage: the sounds were conducted to a conventional stethoscope headset by a length of wide calibre pressure-tubing which passed through the wall. Readings were made at intervals of 30 seconds; the regularly repeated smooth inflation of the cuff did not damage the patient's arm nor prove uncomfortable during interview. The same operator recorded the readings throughout each individual session and indeed the vast majority of all recordings in the entire project were carried out by one person (G.I.). The interview was recorded throughout on a high-fidelity tape recorder: this recording was later transcribed by a secretary on to specially designed sheets showing the time relation of the interview material to the physical variables, in 30-second epochs (see Figure 1).

*Heart Rate.* This was obtained from a Lead II electrocardiogram recorded on one channel of a four-channel pen oscillograph which ran continuously. The number of beats and fractions of a beat were counted in each 10-second epoch, and expressed as a rate per minute.

*Electroencephalogram.* The EEG was recorded from two small silver-silver chloride button electrodes attached by collodion to the scalp over the left

| $\delta$ | $\theta$ | $\alpha$ | $\beta$ | Pulse | B.P. | Name: James M—.                                                                                                           |
|----------|----------|----------|---------|-------|------|---------------------------------------------------------------------------------------------------------------------------|
|          |          |          |         |       |      | 64.                                                                                                                       |
| +        |          |          |         | 76    |      | ... and it was seconds before I had the sense to jump clear.                                                              |
|          |          |          |         |       | 152/ |                                                                                                                           |
| +        | +        |          |         | 72    | 110  | Was it still going?<br>Yes—No, it wasn't.<br>You'd stopped it now?                                                        |
| ++       | +        |          | +       | 76    |      | I didn't stop her though. I was still sitting you see, and it went dry of petrol, and I went as white as anything.        |
|          |          |          |         |       |      | 65.                                                                                                                       |
| +        |          |          | +       | +     | 70   | And the boss was up at the time. His car was sitting at the front of the garage ...                                       |
|          |          |          |         |       | 160/ |                                                                                                                           |
|          |          |          | +       | +     | 73   | 114 and I just narrowly missed it. I ran ...                                                                              |
|          |          |          | +       | +     | 72   | well I didn't run because I was in two minds whether to go back into the garage or go away and leave everything.          |
|          |          |          |         |       |      | 66.                                                                                                                       |
|          | +        |          |         |       | 73   | Yes.<br>Just as it was. But I plucked up courage ...                                                                      |
|          |          |          |         |       | 164/ |                                                                                                                           |
| +        | +        |          |         |       | 72   | 118 and went in. Well, I didn't go to the foreman, I told another chap to tell the foreman. I was frightened to tell him. |
|          |          |          |         |       |      | And he came running out and there was a diesel tractor—easily started the diesels—and he started her up ...               |
|          |          |          |         |       | 82   |                                                                                                                           |

FIG. 1.—Sample of recording sheet.

temporal lobe; bipolar recording technique was used, with the ear as the earthing point. The primary trace was recorded on the pen oscillograph and the signals were also fed to an Ediswan Wave Analyser. The temporal lobe was selected on the basis of existing work (Chapman *et al.*, 1950) as one of the areas most likely to demonstrate any possible change in connection with emotional alterations.

*Synchronization.* In order to synchronize the interview material with the recorded variables, two microphones in parallel were employed; one in the interview room, the other in the observation room. The main function of the latter was to record the passage of each 30 seconds by a low-pitched buzz, and the 10-second and 20-second intervals by a high-pitched buzz: these were superimposed on the tape while the interview was being recorded from the other microphone.

In addition, the time marker actuating the 30-second buzzer also activated a marker pen on the oscillograph trace, and an electromagnetic counter. The start of each 30-second epoch, therefore, was demarcated by (1) a buzzer note on the tape recording, (2) a signal on the marker-pen of the trace, and (3) a serial epoch number on the counter.

The observer who was taking the blood-pressure readings called out the figures to an assistant who noted them on the oscillograph trace, together with the epoch number, at the point where the signal marker was actuated; these verbal observations were of course also superimposed on the tape recording via the parallel microphone.



## ADDITIONAL INVESTIGATIONS

*The Breath-holding Test.* Devised by Ayman and Goldshine (1939), this test depends on the assumption that hypertensive subjects are sensitive to stimuli such as oxygen lack or to increased carbon dioxide, and a higher mean rise in pressure was found by the authors in hypertensives. In the present simplified modification of this test, the subject was asked at the conclusion of the interview to take in a breath and hold it for 30 seconds; the blood-pressure was measured just before inhalation and at the end of the 30-second interval.

*Minnesota Multiphasic Personality Inventory.* This standard psychological test consists of 550 cards bearing statements of various sorts. The subject is asked to place each card into one of three categories—*True, False* or *Cannot Say*, as he thinks they apply to himself. On analysis, the test gives a score of ten personality variables—hypochondriasis, depression, hysteria, psychopathic deviation, masculine/feminine balance, paranoid traits, obsessionalism, schizophrenia, mania and anxiety. Weighted scores of up to 70 for each factor (that is, within 2 standard deviations from the mean of 50) are accepted as within normal limits, but higher scores must be treated with suspicion and are probable indications of personality abnormality.

*Mental Arithmetic.* Introduced at first as an intended "control" for intellectual stimulation, the task of mental arithmetic was found in a number of subjects to be in fact a powerful pressor stimulus. Set the task of serial subtraction of 7 from 100 (93, 86, 79, 72 . . . etc.) two hypertensive subjects for example showed increases of blood-pressure as follows:

from 146/92 to 186/104  
from 180/120 to 216/136

As an aside, we may mention another pressor stimulus which, although described before (Bordley and Eichna, 1938) was not known to us at the outset. This is the desire to micturate; in one hypertensive patient, for example, the blood-pressure climbed steadily throughout interview from 214/124 to 260/134, before we realized that he was experiencing urinary urgency. After relieving himself, the pressure (despite the effort of getting up and walking along the corridor) fell again to the original value of 212/126.

*Plethysmograph.* In the latter part of the project a number of subjects were given finger plethysmograph recordings during the course of the procedures outlined above. The right index finger was held in a perspex cylinder with as little "dead space", as possible, and the cylinder was joined by 1½ metres of fine polythene tubing to a tambour bearing a small surface-silvered mirror. A slit lamp, focused on the mirror, gave a fine beam which was reflected and, after a total throw of 3 metres, registered on a Cambridge recording camera. This apparatus proved sufficiently sensitive to give a good outline of pulse waves, but for prolonged recording the film speed had to be reduced and only finger volume and pulse amplitude were considered. No attempt was made in this study to control temperature or other random variables.

## CONSTITUTION OF CONTROL AND EXPERIMENTAL GROUPS

*Control Group.* This was composed of 40 female subjects drawn from the population of Aberdeen Royal Maternity Hospital: all were at the sixth day following delivery of a healthy live child. The group forms a fairly

representative sample of healthy young women in the region, all social classes being represented. Cases having complications, past or present, were accepted provided the patient was sufficiently fit to be up and about on the sixth day. The mean age of the group was 25.9 years.

*Hypertension of Pregnancy Group.* This group was composed of 25 female subjects, again drawn from the population of the Aberdeen Royal Maternity Hospital; all had in common a rise of blood-pressure in the course of pregnancy. In some, this might have been the only toxic feature, but others showed some or all of the following disturbances—marked weight gain, oedema, headaches, visual symptoms, or albuminuria. All subjects had a variable period of bed rest before taking part in the experiment, and all were permitted at least minimum activity in hospital. The mean age of the group was 26.4 years.

*Psychoneurotic Group.* This was made up of 13 individuals under psychiatric treatment for neurotic disorders. Some were known to have labile blood-pressure, but this was not a criterion for selection and several subjects were normotensive. There were 8 male and 5 female subjects, the mean age being 32.4 years.

*Hypertensive Group.* These were patients under treatment for known hypertension, including patients under care in medical wards, patients with hypertension which was discovered in the course of investigation in the psychiatric units, and hypertensive subjects attending the Blood Transfusion Service as donors. There were 7 males, 22 females; the average age was 53.9 years.

*Plethysmograph Group.* This was a small group of 4 psychoneurotics and 4 hypertensives who were interviewed during the latter part of the research.

## RESULTS

*General.* While it was clearly demonstrated in all groups that variations in blood-pressure and pulse rate occurred during interview, and while it was assumed that the immediate conditions of interview situation must have been responsible for these variations, it was by no means easy to determine the nature of the factors responsible. In line with other researches into this problem, it was thought that a promising approach might be to analyse the emotional significance of the various internal and external events in the interview situation which appeared to be correlated with physical changes.

*Interview Content Analysis.* Previous attempts to describe the events taking place in an interview have been of two sorts—the analysis of topics (such as home life, a love affair, a quarrel, etc.) and second, the analysis of emotions and their control mechanisms (such as rage, fear, repressed anger, etc.).

Early attempts in this study employed methods described by other workers, but no consistent and reliable technique was discovered. For example, each 10-second epoch was graded on a 5-point scale in respect of two variables—"emotional strength", and "degree of repression"; it was hypothesized that higher blood-pressure readings would be positively correlated with "increased emotional strength" and "increased repression". In fact, statistical analysis disclosed no correlation of any sort, and it could not be established that the emotions of rage, anger and fear were positively correlated with pressor responses. However, there was a slight positive correlation between the pressor response and the discussion of the husband by female subjects, and likewise

there was a tendency for the discussion of illness to be associated with raised values.

Overt displays of anxiety or anger during interview were not clearly pressor in effect; and depressive themes (such as the discussion of a bereavement), which might be expected to produce some lowering of values, were not in any way consistent in their effects.

Some observations suggested that the sheer novelty of a topic might produce a pressor response, regardless of its feeling-tone in respect of pleasure or pain. This might indicate that the mechanism at work is *alerting* in nature, and non-specific.

In a more extensive study, all the epochs which were hypertensive (the "peak" epochs), were compared and contrasted for interview content with all the epochs that were hypotensive ("trough" epochs). No clear distinctions were brought out between these two types of epoch in respect of topic, nature of emotional mode of expression, or other psychological variable. However, it was discovered that "peak" epochs contained a significantly greater number of *self-references* ("I", "me", "my", etc.) than the "trough" epochs. The same distinction was found to obtain in the case of the *number of syllables spoken* per epoch, pressor responses being positively correlated with a greater output of syllables per 10 seconds.

The difficulties of correlating "content" with blood-pressure changes are shown in a typical example from a labile subject in Figure 2. Some of the variations are no doubt corrective swings carried out by the homeostatic mechanisms attempting to keep blood-pressure reasonably stable, so it is

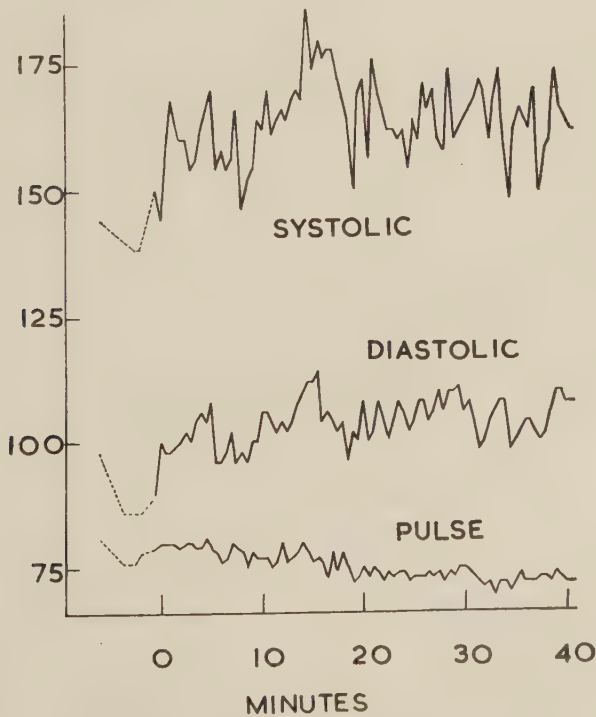


FIG. 2.—Half-minute readings of systolic and diastolic blood-pressure, and pulse rate, recorded from a labile subject.



hard to tell which excursions are primarily responses to an emotional situation and which may be purely physiological.

This particular difficulty, however, was mitigated by our practice of making a smoothed curve of blood-pressure readings; that is, each reading was averaged with the one before and the one after. When the same interview data is redrawn using this technique, as in Figure 3, the trend is more apparent.

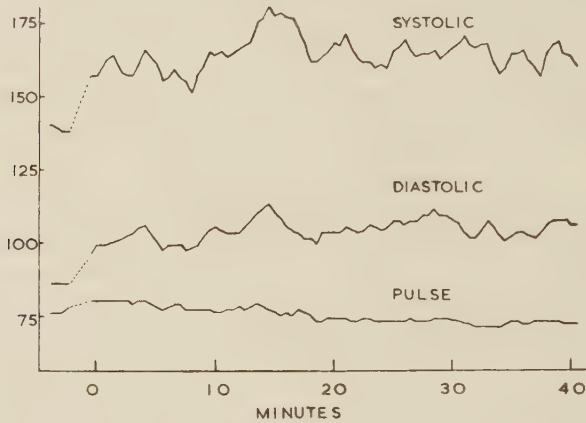


FIG. 3.—The same data as Figure 2, re-drawn as a smoothed graph.

At the start of the major rise the patient was talking about his frustrations and humiliations at work, which had led up to a suicidal gesture.

Content analysis, therefore, remains a formidable task, and no entirely satisfactory method has so far been worked out. One explanation for this is that the *significance* of any given event, whether internal or external, physical or psychological, is highly individual or idiosyncratic in character and cannot readily be equated with factors common to all subjects and exerting similar and predeterminable effects.

**Blood-pressure.** The individuals within each group differed markedly in their response to the interview situation, but nevertheless there are also well-marked group differences.

The Control group showed an almost symmetrical rise and fall in response to the stress of the interview. Figure 4 shows the mean values: the relatively low resting pressure, the increase at the start of interview, the gradual fall as interview progresses, and the return to a low resting value again after its conclusion. It is of interest that the diastolic pressure is comparably affected; in fact, *if considered as a percentage increase, the diastolic response is actually greater than the systolic.*

The Hypertension of Pregnancy group shows an equally symmetrical rise and fall, but all pressures are at a higher level.

The psychoneurotic group shows about the same degree of pressure elevation as the Hypertension of Pregnancy subjects, but the rise in pressure during interview tends to be more sustained and there is not the same symmetrical reversion to normal as was found in the two previous groups.

The Hypertension group operates, of course, at a very much higher level of pressure, and here the tendency to *sustained elevation* is again marked; maximum values are not reached until 20 minutes after the start of the interview, and the resting values after interview remain very high. Taking cases

with interviews of more than 35 minutes duration, it is noted that the rise in pressure is maintained until the end of the interview; and after the interview is discontinued, the resting value then obtained is considerably higher than the one recorded before the start of interview. There is a similarity of behaviour, therefore, in the Psychoneurotic and Hypertensive groups insofar as pressure, once elevated, tends to remain high throughout the interview, and indeed afterwards.

In each case, in every group, there was some rise in blood-pressure at the start of interview; sometimes this rise might be only slight, but increases of more than 30 mm. within the first minute were recorded. Even in the Control group—although some subjects were very stable throughout, others showed fluctuations during the course of the interview of as much as 40 mm.

*Pulse Rate.* The heart rate was found also to vary greatly during the course of interview, and in general it was found that a rise in blood-pressure was accompanied by an increase in heart rate. An indication of the mean results for the Control group is seen in Figure 4, where the pulse rate figures are displayed along with the blood-pressure changes.

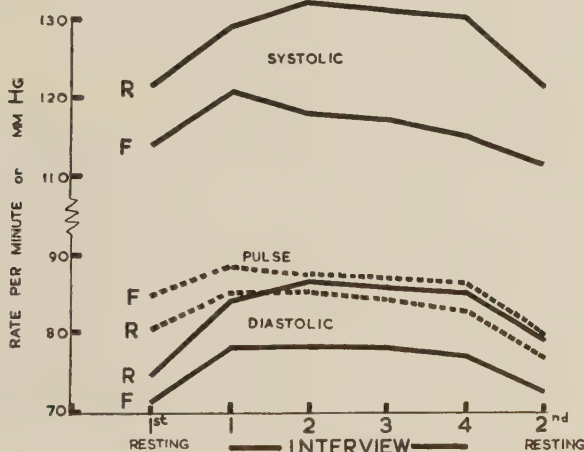


FIG. 4.—Control Group. Mean blood-pressure and pulse rate for the rest periods before and after interview, and for each quarter of the interview.

However, when the mean values for each individual interview were compared, it was found that in each group there tended to be an inverse correlation between the pulse rate and the blood-pressure. That is, *the subjects with the higher blood-pressures tend to have slow pulse rates; but under interview stress, both values tend to increase.*

As regards the mean pulse rate, the Controls take up an intermediate position, the Psychoneurotic group having the slowest pulse rate and the Hypertension of Pregnancy group the fastest. There is some increase in pulse rate in pregnancy in any case, so it is difficult to assess what effect the accompanying hypertension may have had on the pulse rate in these patients. Incidentally, the Hypertension of Pregnancy group was the only one which showed a tendency to continued increase of pulse rate as the interview progressed; in all others it tended to decrease after the initial rise.

Another point was that subjects could be classified according to whether the blood-pressure, during the second quarter of the interview, showed a fall

thereafter or a continued rise. Study of the "fall" and "rise" subgroups showed that there was a significantly higher pulse rate in the "fall" group.

*Electroencephalogram.* This was concerned with detecting any possible EEG changes associated with pressor responses. When the subject reacts to part of the interview with emotional tension and a pressor response, this is presumably organized somewhere in the central nervous system. Is this response, then, capable of being correlated with any detectable change in the EEG as recorded by surface electrodes?

In the records obtained from the Control group there was no consistent change of frequency associated with peaks or troughs in the blood-pressure estimations, but there was a tendency for pressor periods to be associated with the appearance of slow rhythms. However, there is no certainty that these were of true cerebral origin, and they could have been due to artefacts such as movement or sweating, only indirectly linked up with the pressor response. Again, no consistent change was seen in the records of Hypertension patients which were found suitable for analysing; no increase in slow rhythms was observed during pressor epochs and there was no sign of a suppression of alpha activity (as compared with a control group), as has been described elsewhere (Subbotnik and Shpil'berg, 1953; Ackner and Pampiglione, 1957). Similarly no consistent findings, or correlation with pressor epochs, were discovered in the Psychoneurotic group: one subject in this group had EEG records from four separate interviews, and even in this case no characteristic common features were found in the response to stress.

*Breath-holding Test.* This test is considered to show perhaps the highest pressor response which can be produced by deliberate physiological stress. However, in all four groups the mean breath-holding level was exceeded by the mean highest readings found in the course of interview. The highest interview blood-pressure readings represent a percentage increase over the breath-holding values as follows—Controls, 3.9 per cent.; Hypertension of Pregnancy, 4.1 per cent.; Hypertension, 4.9 per cent.; Psychoneurosis, 7.5 per cent.

*It seems therefore that the random emotional stresses imposed by interview possess a greater pressor effect than the deliberate physiological stress invoked by breath-holding; and that the Psychoneurotic group demonstrate the greatest lability of blood-pressure to such interview stresses.*

*Personality Inventory.* The mean scores returned by the Control group for each personality factor lie within normal limits. The five Control cases with the highest mean systolic pressure during interview were compared with the five cases with the lowest systolic pressures; the subjects with low pressures showed scores which were slightly (but not significantly) higher on the obsessional and anxiety ratings. Similar results were found in the Hypertension of Pregnancy group.

The Hypertension group also had normal mean scores throughout, but they tended to score a little higher than the previous groups on the vectors for hypochondriasis, depression and hysteria.

As was to be expected, only the Psychoneurosis group returned abnormal mean scores (on the depressive and obsessional vectors), but their scores on all vectors were high in comparison with the results of the other groups.

*Plethysmograph.* The plethysmograph study was limited to 4 hypertensive and 4 psychoneurotic cases, in addition to one case which was made the subject of a special investigation and interviewed on 24 occasions.

In all cases there was a marked vasoconstrictor response as soon as the interviewer entered the room, and this was associated with an increase in blood-



pressure. As the interview progressed there was, in general, a gradual increase in the pulse amplitude, but the blood-pressure remained at the higher level. *In many of the interviews there were several short periods (up to about half a minute) when vasoconstriction appeared, and these were invariably associated with peaks in the blood-pressure* (see Figure 5). At the end of the interview there

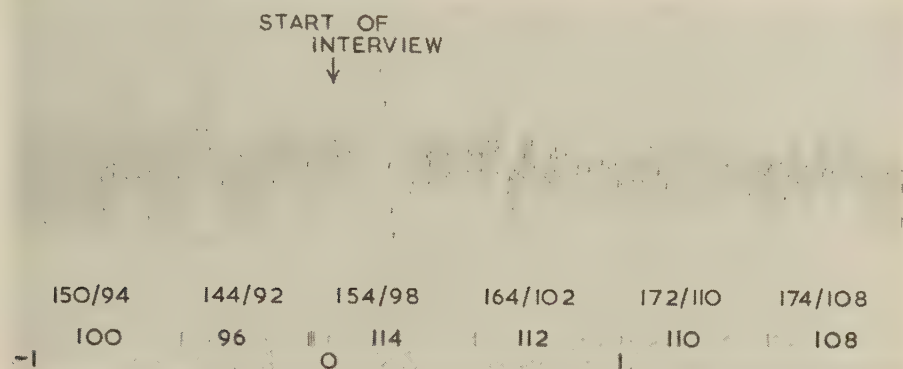


FIG. 5.—Sample of plethysmograph showing vasoconstriction accompanied by rise in blood-pressure.

was always an increase of the amplitude of the pulse waves—representing a vasodilatation—and this was associated with a decrease in the blood-pressure.

These changes might be explained in terms of the following hypothesis.

Sympathetic stimulation at the start of the interview results in secretion of adrenaline from the adrenals and nor-adrenaline from the nerve endings. The nor-adrenaline acts first producing a vaso-constriction and increase in blood-pressure for a certain time, before the concentration of adrenaline builds up in the circulation. Thus the high blood-pressure is maintained while vasoconstriction decreases—but only relatively slightly. Whenever there is a fresh stimulus this sequence of events is repeated. At the end of the interview there is a decrease in both adrenaline and nor-adrenaline.

#### SPECIAL INVESTIGATION

The subject of this study was a woman aged 38 with hysterical symptoms, who was found at routine medical examination to have high blood-pressure readings. In all, she was seen on 24 occasions and usually by the same doctor (W.M.M.), but an interview was not carried out every visit. She showed marked differences in blood-pressure from session to session, the mean resting values prior to interview varying from 125/82 mm. to 172/111 mm., and the mean values for the interviews varying from 152/102 mm. to 201/135 mm.

The first visit was mainly for the purpose of introducing the patient to the experimental set-up, but she had an abbreviated interview with one of the doctors (G.I.) and was given several short intelligence tests. These were found to produce an increase in blood-pressure, as did the breath-holding test.

The next six interviews were carried out by another physician (W.M.M.), the first being diagnostic in type, followed by two sessions of free association, then two of free association plus reassurance, and one of free association plus some “insight” interpretation. During all these interviews there were marked blood-pressure variations, but no single subject of discussion was consistently found to produce a pressor response.

In the eighth interview two selected short passages from previous interviews were replayed to the patient: the first was selected because at the original interview it had evoked a relatively hypotensive response, whereas the second had produced a marked rise in blood-pressure. These passages from the recorded interview were replayed to the patient on an A-B-A-B-A pattern with a few minutes rest between each section. Both passages produced an increase in blood-pressure at the first replay, and the response to the "hypertensive" passage was the higher although it did not reach the level of the original interview. Further repetitions had only a slight effect on the blood-pressure.

The next interview consisted of free association plus "transference" interpretation, and this was followed by a session when the patient was shown *Thematic Apperception Test* cards. In this test the patient is shown pictures of various possibly stress-inducing situations and has to tell a story about each one. All pictures produced a marked increase in blood-pressure, and about this time it began to be noted that there was a definite positive correlation between the height of the blood-pressure and the number of syllables spoken by the patient in a given time. No matter the subject of the conversation, the more the patient spoke the higher were the blood-pressure readings. This finding was later confirmed in all the interviews which followed.

The next two sessions (the 11th and 12th) were conducted by another doctor (G.I.) and the patient was asked to read passages from various books, some thought to be perhaps stressful. There was an increase of blood-pressure during the reading, but no significant differences according to the content. The resting blood-pressure values at the 11th interview were the lowest found on any occasion; the physician (W.M.M.) had started the patient on meprobamate before going on vacation.

The physician (W.M.M.) returned for the 13th interview and discussed with the patient her progress in general terms; this was followed by another session of free association and "transference" interpretation. In the course of the next 4 interviews intravenous sodium amytal was given (7 ml. of 2.5 per cent. solution injected at the rate of 1 ml. per minute). On all occasions the blood-pressure fell during the injection to approximately the resting value for that interview, but rose again as soon as the injection was discontinued.

The 19th interview was again on the lines of "transference" interpretation. The 20th session gave resting and interview blood-pressures higher than on any previous occasion (up to 220/150 mm.), and the patient had obviously been greatly distressed by reading in a Sunday paper that "*The Doctor*" had said that variable blood-pressure was more serious than sustained high pressure.

The 21st interview was interesting in that the physician was delayed by a minor accident. The patient was seen instead by another doctor (G.I.), who gave her the details of this accident without producing any elevation in blood-pressure. Some "sound-effect" records were then played to her, again with no pressor effect, but the unexpected entrance of the physician (W.M.M.) produced a rise of pressure from 152/100 mm. to 192/116 mm. within half a minute.

In all sessions the entrance of the interviewer produced a rise in pressure and pulse rate, associated with evidence of vasoconstriction as discussed previously; but all these changes were more marked when the physician (W.M.M.) was present than with other members of the staff.

The pulse rate was fastest at the start of the interview and gradually tended to become slower as the interview progressed; the pulse rate of the rest period after interview was invariably slower than the value for the rest period

before interview. No such consistent pattern was observed with the systolic or diastolic blood-pressures. It was found, however, that when the resting period before interview was considered, the variations in blood-pressure were as great from one occasion to another, as from the lowest to the highest values in any individual interview.

From this it may be concluded that significant alterations in blood-pressure occur in response to sustained events in the life situation, as much as to transient emotional causes arising during the interview. It is therefore possible that two types of pressor factors are at work in the emotional sphere—one which is *sustained*, and pervasive throughout the life situation for hours, days, or longer; and another which is *transient*, a response to brief episodes probably of an unexpected nature, and producing a rapid alerting reaction. If so, then our observations suggest that both factors are of approximately equal potency.

#### SUMMARY

In an investigation of blood-pressure changes during interview, it was found that random emotional stresses were uncovered which had potent pressor effects in normal controls, in hypertensives and in neurotics. It was notable that the diastolic increases were proportionately greater than the systolic, and that those random emotional stresses on average possessed more pressor effect than a deliberately imposed physiological stress such as breath-holding. Certain individuals also showed marked pressor responses to varied stimuli such as being asked to do mental arithmetic, or the desire to micturate.

All subjects showed an increase in systolic and diastolic pressures at the start of interview; in the control group this tended to level off symmetrically as the interview closed, but the hypertensive and neurotic groups showed a sustained rise of pressure and the resting levels after interview did not fall as low as the pre-interview resting values.

No consistent topics were found to be pressor in effect, but it appeared that pressor responses occurred (1) with novel or "alerting" stimuli; (2) when the subject talked about herself, about illness or about her husband; (3) when the subject's verbal output increased.

The heart rate tended to increase along with the blood-pressure, but subjects having higher blood-pressure levels tended to have slower heart rates.

Finger plethysmography showed that peripheral vasoconstriction accompanied pressor responses, and vasodilatation occurred as blood-pressure fell.

A neurotic patient with labile blood-pressure was interviewed on 24 occasions, and several unusual features are described.

No constant or reliable association was discovered to exist between the temporal electro-encephalogram and the blood-pressure changes.

It is concluded that two types of emotionally-caused pressor responses may exist; one which may be keyed to the life-situation and is sustained in effect over a period of hours or days or longer, and another which is more transient and may represent a non-specific alerting reaction.

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# A CONTROLLED TRIAL OF ETHYLCROTONYLUREA

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## INTRODUCTION

OVER the past few years, there has been an increasing interest in drugs having a tranquillizing or ataractic effect on the central nervous system. Pharmaceutical houses, both here and on the other side of the Atlantic, have vied with one another to be the first to introduce the perfect tranquillizer, providing relief from tension and anxiety with no unpleasant or dangerous side-effects or tendency to addiction, and at the same time if possible to effect an improvement in the management of, if not the cure of, the psychoses.

An initial enthusiasm for these drugs, based on inadequate clinical trials and backed by a large advertising campaign, has in many cases been followed by disillusionment, both in the effects of a drug when carefully compared with a placebo and in the later description of undesirable actions and side-effects.

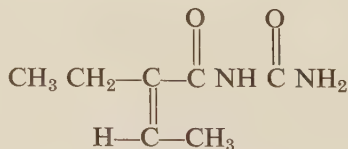
It was therefore particularly stimulating to be given the opportunity of investigating a new compound, the low-melting isomer of ethylcrotonylurea, by means of a double-blind controlled clinical trial before a decision was made whether or not to add this drug to the many similar ones already on the market.

The report which follows details the results of the comparison of the new drug with chlorpromazine and a placebo in a group of chronic psychotic in-patients. This study forms part of a larger investigation, as yet incomplete, which includes out-patients and in-patient neuroses.

## ETHYLCROTONYLUREA

### *Pharmacology*

This substance is an unsaturated open-chain ureide and has the following structural formula:



In previous studies (reported below) in America, the high-melting isomer was used. The manufacturers of the drug in this country believed that the low-melting isomer might offer certain advantages and this form of the drug was used in the present trial.

Preliminary laboratory investigation (Ross, A. F., 1959) gave the following results:

### 1. *Toxicity by Mouth*

#### (A) *Acute Toxicity*

Acute LD<sub>50</sub> determination, made in albino mice:

High Melting Isomer 3.0 gm./Kg.  $\pm 7$  per cent.

Low Melting Isomer 1.7 gm./Kg.  $\pm 7$  per cent.

#### (B) *Toxicity on Repeated Dosage*

In a controlled study on young male albino rats, there were no deaths attributable to the drug when given in doses of up to 400 mg./Kg. of the low-melting isomer five days a week over a period of twelve weeks. Percentage weight increase in rats receiving ethylcrotonylurea was less than that of the controls but it was considered that this might have been due to the sedating effect of the drug which was apparent in high dosage. Histological examination of the stomach, liver, kidney, adrenal, spleen, heart and lung revealed no pathological change.

### 2. *Hypnotic and Sedative Effects*

#### (A) *Hypnotic Effect in Mice*

The oral Hypnotic Dose<sub>50</sub> was:

High Melting Isomer 2.3 gm./Kg.  $\pm 9$  per cent.

Low Melting Isomer 1.4 gm./Kg.  $\pm 6$  per cent.

From these studies it will be seen that while the low-melting isomer is slightly more toxic it has also a slightly greater hypnotic activity. The onset of effects after oral administration was more rapid; thus, it is probable that its greater toxicity and hypnotic effects are due to more rapid absorption.

#### (B) *Extension of Barbiturate Sleeping Time*

Mice pre-treated with both isomers of ethylcrotonylurea showed a definite increase in barbiturate sleeping time but there was considerable individual variation in response.

#### (C) *Effect on Spontaneous Activity*

Spontaneous nocturnal activity of the rat was studied by means of an activity cage constructed so that each movement of the rat completed an electrical circuit actuating an electro-magnetic counter. Oral administration of 400 mg./Kg. ethylcrotonylurea reduced the spontaneous activity of the rat by about 50 per cent. It is known that chlorpromazine is active in this test at an oral level of 5 mg./Kg.

Sedation is estimated to occur at 25 per cent. of the acute toxic dose as compared with 50 per cent. in the case of phenobarbitone and 64 per cent. with meprobamate. Hypnotic effects occur at 82 per cent. in the case of the low-melting isomer and 77 per cent with the high-melting isomer, the latter figure being slightly lower than that reported by American workers (Lim *et al.*, 1956).

Thus, in the late appearance of hypnotic effects as compared with the acute toxic dose, ethylcrotonylurea tends to resemble chlorpromazine and reserpine.

### *Indications*

Early studies in the United States had suggested that this drug was particularly useful as a calmate in patients who were subject to abnormal behaviour

due to anxiety and tension, and that moderately overactive patients might benefit from doses of from 100 to 300 mg. three times a day. The manufacturers of the drug in this country were hopeful that it might have some specific beneficial effect on the behaviour of psychotic patients in addition to its action on tension and anxiety.

### *Dosage and Administration*

The drug is administered orally, and in human subjects has been given up to 1,800 mg. daily. In the present trial, it was supplied in 100 mg. tablets and was given up to a maximum of 1,200 mg. per day, as in a previous series of cases in America reported by Ferguson and Linn (Ferguson *et al.*, 1956), it had been found that doses of more than 900 mg. did not produce significantly different results.

Occasional side-effects such as rash, nausea, dizziness or drowsiness have been reported, but blood, urine and liver function investigations have all been within normal limits, and no changes in the pulse, respiration, temperature or blood-pressure have been reported even in a patient to whom 5.4 g. of the drug had been accidentally administered.

### METHOD

It was decided to select a group of 25 chronic psychotic patients from the total population of the female side of the hospital, less the following categories:

- (a) Patients of under two years stay.
- (b) Epileptics.
- (c) Patients suffering from intercurrent physical illness on whom the participation in such a trial might have a deleterious effect.

The patients selected, who thus represented a small cross-section of the chronic hospital population, had the following characteristics:

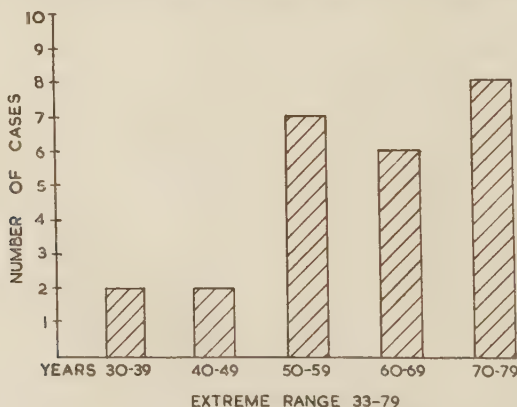


FIG. 1.—Age range of therapeutic group.

In order to be able to allow for any possible general shift in the hospital population towards better or worse behaviour due to circumstances outside the trial, a control group of 30 patients was rated at the beginning and the end of a twelve-month interval which covers the period of the trial.



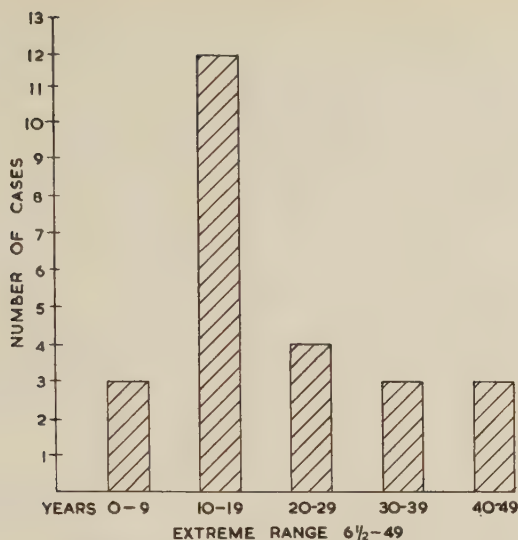


FIG. 2.—Length of stay in hospital of therapeutic group.

TABLE I  
Diagnoses of Patients in Therapeutic Group

|                          |    |    |    |    |    |    |    |    |    | Number<br>of Cases |
|--------------------------|----|----|----|----|----|----|----|----|----|--------------------|
| Schizophrenia:           |    |    |    |    |    |    |    |    |    |                    |
| Simple                   | .. | .. | .. | .. | .. | .. | .. | .. | .. | 6                  |
| Hebephrenic              | .. | .. | .. | .. | .. | .. | .. | .. | .. | 4                  |
| Catatonic                | .. | .. | .. | .. | .. | .. | .. | .. | .. | 4                  |
| Paranoid                 | .. | .. | .. | .. | .. | .. | .. | .. | .. | 7                  |
| Involutional melancholia | .. | .. | .. | .. | .. | .. | .. | .. | .. | 2                  |
| Manic-depressive illness | .. | .. | .. | .. | .. | .. | .. | .. | .. | 1                  |
| Senile psychosis         | .. | .. | .. | .. | .. | .. | .. | .. | .. | 1                  |
| Total                    | .. | .. | .. | .. | .. | .. | .. | .. | .. | 25                 |

## COMPARISON OF EFFECTS

The effects of ethylcrotonylurea were to be compared with those of chlorpromazine and a placebo. These three substances were supplied in matching tablets by Messrs. Smith & Nephew, the sponsors of the new drug. Each chlorpromazine tablet contained 25 mg. of the drug, the ethylcrotonylurea 100 mg., and the placebo 325 mg. of lactose.

Each patient was to act as her own control and would thus receive each of the three substances consecutively, the order of administration being determined by random selection. The period of administration of the drug was to be 5 weeks in each case, leaving an interval of one week between each drug. The instructions for taking the tablets were similar in each case, namely, two tablets three times a day for the first week and four tablets three times a day for the following four weeks. This scheme gave the following total dosage:

Chlorpromazine, 150 mg. daily for the first week, 300 mg. daily for the next four weeks.

Ethylcrotonylurea, 600 mg. daily for the first week, 1,200 mg. daily for the next four weeks.

Placebo (Lactose), 1.95 and 3.90 gm. daily, respectively.

The total number of tablets for each five-week period (378) were put in a separate envelope, labelled "A", "B", or "C" and a code was kept showing

which tablets any patient was taking during any given period. The code was to be used only in the event of an emergency occurring during the course of the trial. It was thus possible to keep the handling and the knowledge of the identity of the tablets under the control of a person other than the psychiatric assessor of results until the trial was completed.

It was considered that if there was to be any marked beneficial effect from ethylcrotonylurea, this would probably become obvious within the five-week period. This was suggested by the experience of Charmian Elkes (Elkes, 1957) in reporting rauwolfia trials in chronic psychotics, which shows that in most cases likely to gain much improvement, this occurs within five weeks. This view has also been more recently supported in the case of chlorpromazine by J. Crawford Little (Little, 1958) who shows that, contrary to the commonly held view that chlorpromazine does not exert its full effect until it has been given for six weeks, such effect as it does have is equally apparent within three weeks.

It was arranged that the patients who were already having tranquillizing drugs of any kind should discontinue these for a period of at least two weeks before the beginning of the trial.

#### METHOD OF ASSESSMENT

In order to assess the improvement or otherwise of the group of chronic psychotic patients, an objective method of rating their behaviour which could be treated statistically was desirable. For this purpose, the Parkside Behaviour Rating Scale (P.B.R.S.) was selected. This has been described in full by K. E. Schmidt (Schmidt, 1957) and has the advantage of being simple to administer, extremely reliable as shown by significance tests, and well validated by experience.

Briefly, each of six behavioural characteristics is rated on a five-point scale. The characteristics are:

- (a) Self care.
- (b) Orientation as far as communicated.
- (c) Communication and socialization.
- (d) Psychotic behaviour.
- (e) Co-operation and occupation.
- (f) Mood and reaction to environment.

Thus, the worst possible behaviour would carry a rating of six points, as against a maximum of thirty points for a model patient.

#### CONTROL GROUP

The patients in the control group were selected in exactly the same manner as those in the trial group, and constitute a similar random sample of the chronic hospital population.

TABLE II  
*Diagnoses of the 27 Patients Rated in the Control Group*

|                          | No. of Cases |                                                               |
|--------------------------|--------------|---------------------------------------------------------------|
| Schizophrenia .. ..      | 18           | (1 spontaneous recovery, sent on indefinite leave)            |
| Involucional melancholia | 3            |                                                               |
| Manic-depressive illness | 1            |                                                               |
| Senile psychosis .. ..   | 1            |                                                               |
| Senile dementia .. ..    | 2            | (including 1 patient who died during the year)                |
| Mental defective .. ..   | 2            | (including 1 patient who was transferred to another hospital) |
| Total .. ..              | <u>27</u>    |                                                               |

Three of these control patients died before the first assessment was made, leaving 27 for rating, and during the twelve-month period, one further patient died, one was transferred to another hospital, and one recovered and was sent on indefinite leave. The average P.B.R.S. rating of the control group was 18.8 points. At the end of twelve months, the shift was less than 0.1 points of P.B.R.S., an insignificant change.

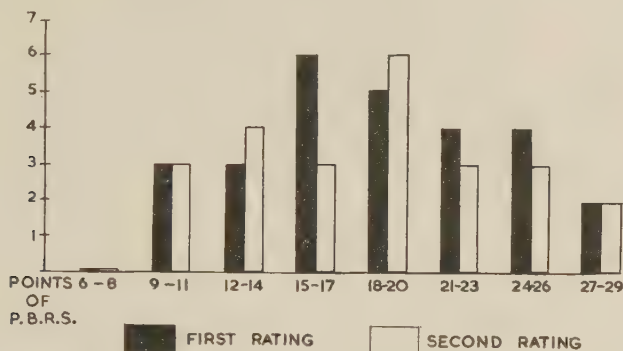


FIG. 3.—Rating and re-rating of the control cases with an interval of one year.

The standard deviation between rating and re-rating was 3 points of P.B.R.S., and a significant improvement or deterioration over the earlier rating would require, at the 5 per cent. level, a movement of at least 5 points. Only four patients qualified for this distinction. Three were significantly worse. Of these, one had a recurrent depression at the time of the second rating; one sustained a fractured femur; the third became bedridden due to senile cardiovascular degeneration, and increasing dementia.

The fourth patient, who improved, was a chronic schizophrenic, disturbed at the time of the first rating and refusing food; her improvement followed a short course of electrical treatment and was maintained at the second rating.

The inference to be drawn from this control group, therefore, is that there was no significant shift in behavioural characteristics in the chronic hospital population over the period of the trial.

#### THERAPEUTIC GROUP

##### ANALYSIS OF RESULTS

A complete analysis of the rating and re-rating of these patients after chlorpromazine, ethylcrotonylurea and the placebo is shown in Figure 4 on page 857.

The order in which the drugs were given is indicated in Table III in parenthesis. Diagnoses and any side-effects are shown in each case. There were no deaths in this group, but one patient (Case 120) was so unco-operative in taking tablets that it was decided to abandon the attempt, in her case.

The average rating of the group before treatment was 17.3 points of P.B.R.S. The average shifts in P.B.R.S. are as follows:

- After placebo: 0.25 points (increase).
- After chlorpromazine: 0.45 points (increase).
- After ethylcrotonylurea: 0.2 points (decrease).

As the standard deviations were around three points from the original rating, only shifts of plus or minus five points could be considered significant. A change



TABLE III.  
Analysis of the Therapeutic Group

| Case Numbers   | Diagnosis | Preliminary |         |       |        | After Placebo |          |       |         | After Chlorpromazine |        |              |       | After Ethylcrotonylurea |       |         |       |
|----------------|-----------|-------------|---------|-------|--------|---------------|----------|-------|---------|----------------------|--------|--------------|-------|-------------------------|-------|---------|-------|
|                |           | P.B.R.S.    | B.P.    | Hb. % | W.B.C. | Order         | P.B.R.S. | Shift | B.P.    | Hb. %                | W.B.C. | Side-Effects | Order | P.B.R.S.                | Shift | B.P.    | Hb. % |
| 101 Sch. S.    |           | 14          | 160/110 | 96    | 6-350  | (2)           | 10       | 4     | 160/80  | 96                   | 7-450  |              | (3)   | 16                      | 2     | 160/110 | 91    |
| 102 Sch. S.    |           | 22          | 130/90  | 93    | 5-090  | (2)           | 10       | 4     | 170/90  | 94                   | 9-350  |              | (3)   | 19                      | 2     | 120/90  | 86    |
| 103 Sch. S.    |           | 18          | 200/120 | 95    | 7-125  | (3)           | 23       | 2     | 200/100 | 97                   | 6-100  |              | (2)   | 23                      | 5     | 190/120 | 101   |
| 104 Sch. H.    |           | 11          | 150/90  | 95    | 5-500  | (3)           | 13       | 2     | 120/80  | 87                   | 7-150  |              | (2)   | 22                      | 1     | 140/90  | 94    |
| 105 Sch. P.(D) |           | 20          | 150/90  | 86    | 7-150  | (3)           | 13       | 2     | 140/80  | 85                   | 5-100  |              | (1)   | 20                      | 0     | 150/90  | 92    |
| 106 Sch. H.    |           | 14          | 140/90  | 92    | 7-170  | (3)           | 14       | 0     | 176/96  | 90                   | 7-800  |              | (3)   | 12                      | 2     | 180/110 | 97    |
| 107 Sch. C.    |           | 18          | 170/90  | 102   | 8-670  | (2)           | 21       | 3     | 130/80  | 102                  | 7-750  |              | (3)   | 12                      | 2     | 150/90  | 89    |
| 108 Sch. H.    |           | 22          | 130/80  | 98    | 7-910  | (2)           | 22       | 0     | 180/80  | 98                   | 7-850  |              | (1)   | 24                      | 2     | 120/80  | 89    |
| 109 Inv. Mel.  |           | 22          | 130/70  | 98    | 8-160  | (1)           | 23       | 3     | 160/84  | 94                   | 5-975  |              | (2)   | 25                      | 3     | 130/70  | 93    |
| 110 Sch. C.(D) |           | 12          | 150/100 | 93    | 7-400  | (3)           | 13       | 3     | 200/90  | 94                   | 8-850  |              | (2)   | 13                      | 1     | 180/80  | 92    |
| 111 Sch. P.    |           | 20          | 220/80  | 99    | 9-350  | (2)           | 22       | 3     | 170/100 | 94                   | 5-850  |              | (1)   | 21                      | 1     | 190/80  | 94    |
| 112 Sch. C.    |           | 10          | 120/80  | 91    | 5-100  | (1)           | 12       | 3     | 120/75  | 85                   | 5-750  |              | (3)   | 12                      | 3     | 110/70  | 94    |
| 113 M.-D.      |           | 18          | 160/80  | 86    | 7-500  | (2)           | 15       | 0     | 170/100 | 90                   | 5-750  |              | (3)   | 15                      | 3     | 150/80  | 86    |
| 114 Sch. H.    |           | 20          | 210/84  | 91    | 5-350  | (3)           | 15       | 3     | 120/75  | 85                   | 5-600  |              | (1)   | 19                      | 1     | 110/80  | 95    |
| 115 Sch. P.(D) |           | 15          | 180/130 | 101   | 5-180  | (1)           | 20       | 0     | 170/80  | 86                   | 6-200  |              | (2)   | 19                      | 4     | 210/120 | 97    |
| 116 Sch. S.    |           | 25          | 180/110 | 98    | 9-500  | (3)           | 16       | 1     | 190/120 | 104                  | 10-750 |              | (2)   | 19                      | 4     | 180/70  | 96    |
| 117 Inv. Mel.  |           | 26          | 180/110 | 100   | 9-960  | (2)           | 25       | 1     | 140/90  | 97                   | 7-400  |              | (1)   | 25                      | 1     | 100/70  | 96    |
| 118 Sch. S.    |           | 16          | 160/80  | 100   | 6-960  | (2)           | 17       | 1     | 150/80  | 92                   | 6-300  |              | (3)   | 16                      | 0     | 140/80  | 99    |
| 119 Sch. C.    |           | 18          | 210/110 | 99    | 8-450  | (2)           | 19       | 1     | 170/90  | 95                   | 5-400  |              | (3)   | 19                      | 1     | 160/100 | 96    |
| 120 Sch. P.    |           | 18          | 170/100 | 93    | 6-100  | (2)           | 19       | 1     | 136/76  | 88                   | 5-300  |              | (2)   | 13                      | 3     | 120/68  | 84    |
| 121 Sch. S.    |           | 10          | 112/72  | 93    | 7-800  | (1)           | 9        | 1     | 130/76  | 90                   | 9-350  |              | (2)   | 15                      | 3     | 130/80  | 93    |
| 122 Sch. S.    |           | 14          | 120/80  | 92    | 5-560  | (3)           | 11       | 3     | 130/90  | 95                   | 4-800  |              | (1)   | 27                      | 3     | 140/110 | 88    |
| 123 Sch. P.    |           | 24          | 130/80  | 97    | 5-775  | (2)           | 25       | 1     | 170/100 | 89                   | 8-100  | O            | (3)   | 15                      | 0     | 160/120 | 94    |
| 124 Sen. Psy.  |           | 15          | 201/120 | 104   | 7-150  | (1)           | 17       | 2     | 150/90  | 102                  | 5-800  |              | (3)   | 16                      | 1     | 150/90  | 94    |
| 125 Sch. P.    |           | 17          | 200/100 | 94    | 8-250  | (2)           | 18       | 1     | 150/90  | 102                  | 5-800  |              | (3)   | 16                      | 1     | 150/90  | 94    |

Code

Order in which drug was given, 1st, 2nd, 3rd.  
Points of Parkside Behaviour Rating Scale.

Blood Pressure.

Haemoglobin per cent.

White Blood Cell count.

Side-Effects:

Drowsiness.

Fainting.

Incontinence.

Oedema, Ankles or Face.

Parkinsonian Symptoms.

Vomiting.

Diagnosis:

Schizophrenia

Catatonic

Simplex

Hebephrenic

Paranoid

Involuntal Melancholia

Manic-Depressive Disease

Senile Psychosis

Dementing, due to senile change

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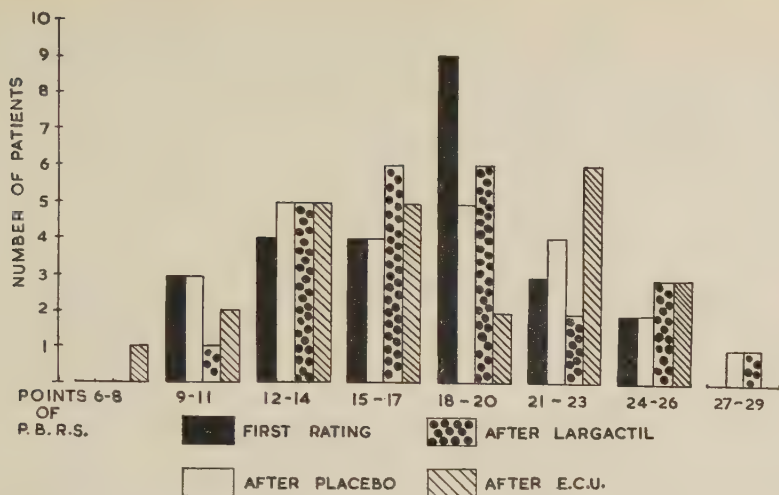


FIG. 4.—Rating and re-rating of trial cases following (1) Placebo, (2) Chlorpromazine (3) Ethylcrotonylurea.

of this order occurred in only four cases, the change being analysed as follows:

*Case 103.* The patient maintained a significant improvement after all three drugs, and since the first drug administered was the placebo, it was considered that the improvement was due to the extra attention given to the patient as a result of the trial, rather than to any pharmacological effect.

*Case 109.* The patient showed a significant improvement after the placebo only. This, again, was the first drug administered, and the patient who was a chronic involutional depressive stated that she felt more lively after it. At the end of the trial, however, she said that she felt much better when she was not taking any tablets at all!

*Case 113.* This was a manic-depressive patient who became significantly worse after the placebo, after a gradual deterioration whilst taking the other two drugs, this downward course being due to a natural swing in her illness.

*Case 114.* This patient became very disturbed, impulsive and offering sudden violence to others. She was a hebephrenic who was subject to periodic outbursts of this kind. This episode started while she was on chlorpromazine, which did not help her in any way, and continued when the drug was changed to ethylcrotonylurea. In the end, she had to be given electrical treatment, and this produced a seven-point improvement in P.B.R.S., but she was still significantly worse at the end of the trial.

## SIDE-EFFECTS

### 1. General

All side-effects, however minor, were recorded. These consisted of:

Drowsiness

Faintness

Oedema (ankle or face)

Vomiting

Parkinsonian symptoms

Incontinence of urine

and were shown by eleven cases out of the twenty-five.

In eight cases, the side-effects occurred during chlorpromazine administration and consisted of drowsiness, faintness, oedema of the ankles and face, vomiting, and Parkinsonian symptoms. Of the two cases on ethylcrotonylurea showing side-effects, one patient had a previous incontinence which became somewhat worse whilst she was taking this drug; the other case had an increase in ankle oedema which was present beforehand. It is therefore probable that these side-effects had nothing to do with the drug. The remaining case showed an increased tendency to ankle oedema whilst on the placebo, this being due to cardiovascular degeneration.

Thus, our experience confirmed the widely held impression that chlorpromazine carries a high risk of side-effects—in this series of cases 30 per cent. of patients were affected whilst on this drug, and included all the more severe reactions of those listed above.

Ethylcrotonylurea, on the other hand, appeared to be devoid of side-effects.

## 2. *Blood-pressure Recordings*

The general picture of the blood-pressure readings is one of lability. Readings were all taken under normal day-to-day conditions, without any special precautions, and in the sitting position. Only marked fluctuations are considered.

In three patients (Cases 119, 124, and 125) the initial blood-pressure was much higher than that during the administration of any of the drugs. This may have been due to the psychological stress of the first blood-pressure examination. In one patient (Case 111) there was a marked fall after ethylcrotonylurea, but this appears to have been due to a continued improvement in the patient who was a paranoid schizophrenic, over the period of the trial, irrespective of the drug taken, the ratings being plus 1 after chlorpromazine, plus 3 after the placebo, and plus 4 after ethylcrotonylurea. There was one marked fall after chlorpromazine (Case 117) and one gain (Case 116). In three other patients (Cases 102, 112, and 113), blood-pressures were higher on the placebo tablets than at the initial rating or after the other drugs.

Thus, it is fairly clear that, in the present series at any rate, there were no marked pharmacological effects on blood-pressure. The expected fall with chlorpromazine did not occur, nor were any significant changes in blood-pressure found with ethylcrotonylurea.

## 3. *Haemoglobin Estimations*

These revealed no significant changes with any of the drugs, the average level varying between 92 per cent. and 95 per cent., the lower figure appearing in the chlorpromazine series.

## 4. *White Cell Counts*

Average white cell counts varied between 6,660 and 7,340, the lesser figure following the placebo and the greater figure occurring after the chlorpromazine, this higher average being partly due to two patients (Cases 114 and 116) both of whom had a white cell count of over 10,000. In Case 114 the cause of this leucocytosis was not apparent, but Case 116 suffered from sun-burn blisters which took some time to clear, and the leucocytosis persisted during the administration both of chlorpromazine and the placebo tablets.

There were no significant alterations in white cell counts arising during the administration of ethylcrotonylurea with the exception of Case 123, who showed a gradual reduction in the count throughout the trial. This could have been initiated by chlorpromazine, but certainly continued during the administration of the placebo. Despite this rather low count, the patient has remained in good physical health and the latest white cell count, taken several months after the completion of this trial and after the prolonged administration of chlorpromazine, was 6,150, the differential count being normal.



## DISCUSSION

Several facts emerge from an analysis of the results in this comparison of ethylcrotonylurea, chlorpromazine and placebo.

Ethylcrotonylurea is a safe drug when administered within the limits recommended by the manufacturer, namely, in doses of up to 1,200 mg. per day. There have been no side-effects which could have been attributed unequivocally to the drug, nor have there been alterations in blood-pressure or haemopoiesis.

On the other hand, ethylcrotonylurea does not appear to have any specific pharmacological effect on chronic psychotic illness, but in this respect, at any rate as far as this trial goes, it cannot be differentiated significantly either from chlorpromazine or placebo.

This tends to confirm the present trend of opinion that factors other than pharmacology may have been responsible for the improvement of patients seen in recent years, and previously wholly attributed to drugs such as those of the phenothiazine series. In this trial, the only patient who maintained a significant improvement (Case 103) did so during the administration of the placebo.

It cannot be too strongly stressed, however, that the group of patients under consideration are psychotic cases of long standing who have already had most of the modern treatments known to psychiatry, including the so-called tranquillizing drugs, and are in their present condition because they have failed to respond to any of these treatments. They therefore represent a highly selected group, and it is not surprising that they fail to show any significant overall improvement.

## SUMMARY

A study is reported of the effect of a new tranquillizing drug, ethylcrotonylurea, on a representative group of chronic psychotic patients by means of a double-blind controlled trial, as compared with chlorpromazine and a placebo.

Alterations in behaviour were assessed objectively by means of the Parkside Behaviour Rating Scale.

A parallel rating of a similar group of 30 control cases was made at the beginning and the end of a twelve-month interval which covered the period of the trial. From observations on this group it could be concluded that there had been no significant alteration in the behavioural characteristics of the chronic hospital population over this period.

Observations were made on side-effects, blood-pressure, haemoglobin levels and white cell counts.

From this study, it is concluded that ethylcrotonylurea is a safe drug when administered in doses of up to 1,200 mg. per day, but that it produces no significant improvement in the behaviour of chronic psychotic patients whose stay in hospital had varied between 6 and 49 years.

Studies of the effects of chlorpromazine tended to confirm the recent trend of opinion that this drug is also of little use in the treatment of this category of patient. Undesirable side-effects followed its administration in more than 30 per cent. of cases, and no patient showed any significant improvement in mental state which could be attributed to this drug.

## ACKNOWLEDGMENTS

My thanks are due to Dr. Leslie Ford, Medical Superintendent of Three Counties Hospital, for his interest in the trial and permission to publish the results; to Mr. E. M. Bavin and Smith & Nephew Research Limited for arranging the preparation and free supply of all the matching tablets of the drugs used in this trial; to Miss B. Billington, Deputy Matron, who undertook the coding and issuing of the tablets; to Mr. Norman Warren and the staff of the Pathology Department for the laboratory investigations; to Mr. H. Kruse for his help in preparing the diagrams for publication; to the Nursing and Clerical staff whose assistance was so readily given; and last, but by no means least, to my colleagues for their helpful criticism and for allowing me access to their patients.

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# THE EFFECT OF ELECTRO-CONVULSIVE THERAPY ON INITIATIVE

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HELPING the senile patient is not easy, and treatment today is largely palliative. Recent cybernetic work (Ashby, 2), however, offered a suggestion that some alleviation might be possible. This paper describes briefly the underlying theory and how we investigated the matter clinically. (Only an outline of the theory can be given here.)

## THE CYBERNETICS OF OLD AGE

The fundamental logic of mechanism is now well founded (Ashby, 3) and sufficiently developed for a good deal to be said about "mechanisms" in general. ("Mechanism" here means whatever is law-abiding and regular in its behaviour; it therefore *includes* psychosomatic and emotional mechanisms so far as they are not merely indeterminate.) So far as neurons are basically law-abiding (and what physiologist doubts this?), so far will the brain be "mechanistic" and subject to the laws of mechanism.

Outstanding in these laws is the fundamental tendency of any system to go to equilibrium. When a pendulum goes to its central position, or a watch-spring goes to the run-down state, the equilibrium is simple, obvious, and uninteresting. But when the system is as complex as a human being, the equilibrium may be equally complex, with partial equilibria, mobile equilibria, equilibrium at a cycle, and so on. A consequence of this fact is that if the system is acted on (disturbed, stimulated) by surrounding conditions, its state at any moment tends to be characterized more by what has happened recently than by what happened earlier—the so-called law of experience (Ashby, 4).

The law implies that if the changes in the surrounding conditions are statistically constant, the response of the system has a fundamental tendency to diminish (Ashby, 5). (An example of conditions that are always changing but which are constant in how they change is given by a recurrent waveform—the tick of a clock for instance.) Thus the well-known and ubiquitous phenomenon of "habituation" (often called "adaptation" when it occurs in a sense organ) is to be expected whenever a mechanism, such as the brain, is subjected to conditions or stimuli that are statistically constant.

Now it is a peculiar virtue of the modern logic of mechanism that its theorems are equally valid whether the system is small or large, and whether the time-interval is brief or protracted. They will therefore be applicable to the whole brain, considered over a life-time. Over such a span, many variations of



stimuli or surrounding conditions will form a statistically constant sequence. Though events never recur exactly, a great deal of life is repetitious: day follows night, and night follows day; when one is young, one encounters new dishes at meal-times frequently—as one gets older, surprises at meal-times get rarer. As one gets older, more and more events are recognized as mere repetitions of what has happened before. Thus, as a person's life goes on, there is a growing tendency towards generalized habituation. The possibility arises that this process, now well understood, may play a major part in the condition known clinically as "senility".

(Senility is sometimes regarded as analogous to the "wearing out" of a man-made machine. Any resemblance can be only superficial: a machine wears out by losing substance that it cannot replace; the living body, on the other hand, is in a steady state at which loss and replacement are closely balanced over many years: a man who gets fatter as he gets older can hardly be said to be "wearing away". Since positive evidence for this concept is practically non-existent, it must be dismissed as little better than a metaphor.)

When a system has arrived at an equilibrium (of whatever type), and is thereby restricted to keeping within some set of states, there are, in general, just two ways by which an external agent can act on it to get it away from the set of states. One method (of little interest to us in this paper) is to make a permanent alteration in the system's conditions or parameters, so as to induce a new field (Ashby, 1); in it, the set of states may be no longer equilibrial, so that the system can move to a new region of states; being leucotomized is such an alteration. The second method (of particular interest here) is to subject the system to some stimulus that is powerful enough to be effective and is also very different from all the stimuli that have arrived before. (The two methods are not mutually exclusive; for if the system contains step-functions, a stimulus that is transient may leave permanent changes on the step-functions, so that the rest of the system is affected persistently by their new values.) If, therefore, the senile patient is suffering from an extreme degree of the process called habituation when it occurs transiently, the giving to such a patient of an extremely unusual stimulus might be expected to restore him to some degree of normality. There were thus reasons for thinking that some senile patients might be benefited to some degree by the giving of a very strong and unusual stimulus. Outstanding in these qualities, of course, is electro-convulsion; and we considered the possibility that the patient who showed the picture of extreme habituation—the cabbage-like—might be favourably affected by its application. We decided therefore to select cases who might be regarded as specially likely to benefit, to divide the group into subgroups by some irrelevant ("random") criterion, and to give the treatment to one subgroup while retaining the other as control.

We did not overlook the fact that the results might throw light on the mode of action of E.C.T.—a question as obscure as ever, even after twenty years of experience and research.

#### THE PATIENTS

For simplicity and uniformity the patients were all women. Excluded were the schizophrenic demented, those aged over 90, and the leucotomized; also excluded were those whose senility might be considered clinically as containing a depressive element, for we did not wish this factor to confuse the issue. We selected primarily those who might be described as excessively stable, cabbage-

like, by the behavioural criterion that they tended to react to ordinary stimuli and events with a reaction of less than ordinary size. (This group must be characterized in this way, for it does not correspond to any generally accepted clinical grouping.) Thus we included cases that showed marked apathy, passivity, and lack of initiative; we excluded those that were restless, aggressive, active in body, or actively deluded or hallucinated.

The subjects' conditions and their changes with treatment were assessed by three independent observers: the medical clinician, the psychologist, and the ward sister. The latter was the chief observer, for she lived with the patients and could detect subtle changes that might elude others. For this purpose a 28-item questionnaire was constructed. The questions, and how they were scored, define what we mean, below, by "clinical improvement" and "initiative". They are given in Table I. (The letters on the right are referred to later.) Each

TABLE I

|    |                                                                                    |    |    |    |    |   |   |
|----|------------------------------------------------------------------------------------|----|----|----|----|---|---|
| 1  | Has the patient been out of bed today?                                             | .. | .. | .. | .. | Y | Y |
| 2  | Has she got out of bed without being asked?                                        | .. | .. | .. | .. | — | Y |
| 3  | Has she washed herself?                                                            | .. | .. | .. | .. | Y | Y |
| 4  | Has she done her own hair?                                                         | .. | .. | .. | .. | Y | Y |
| 5  | Has she fed herself?                                                               | .. | .. | .. | .. | Y | Y |
| 6  | Has she used words like "I want . . . "?                                           | .. | .. | .. | .. | — | Y |
| 7  | Has she found her own way to the lavatory?                                         | .. | .. | .. | .. | Y | Y |
| 8  | Has she been mute?                                                                 | .. | .. | .. | .. | N | N |
| 9  | Has she talked to herself?                                                         | .. | .. | .. | .. | N | Y |
| 10 | Has she been hallucinated?                                                         | .. | .. | .. | .. | N | Y |
| 11 | Has she been destructive?                                                          | .. | .. | .. | .. | N | Y |
| 12 | Has she complained about anything?                                                 | .. | .. | .. | .. | — | Y |
| 13 | Has she resisted being moved (from her chair, or bed, or room)?                    | .. | .. | .. | .. | N | Y |
| 14 | When by herself, has she laughed or cried?                                         | .. | .. | .. | .. | N | Y |
| 15 | Has her mood fluctuated greatly?                                                   | .. | .. | .. | .. | N | Y |
| 16 | If uncomfortable, would she move of her own accord to a better place?              | .. | .. | .. | .. | Y | Y |
| 17 | At meal-times, did she make her own way to the table?                              | .. | .. | .. | .. | Y | Y |
| 18 | At table, did she pass the salt, etc., to the other patients?                      | .. | .. | .. | .. | Y | Y |
| 19 | Did she ask any questions of the Staff?                                            | .. | .. | .. | .. | Y | Y |
| 20 | Did she help the Staff in any way?                                                 | .. | .. | .. | .. | Y | Y |
| 21 | When with others, did she <i>start</i> a conversation?                             | .. | .. | .. | .. | Y | Y |
| 22 | When other patients were active, did she join in with them?                        | .. | .. | .. | .. | Y | Y |
| 23 | Did she interfere with the other patients?                                         | .. | .. | .. | .. | N | Y |
| 24 | Did she do any writing?                                                            | .. | .. | .. | .. | Y | Y |
| 25 | Has she looked at today's newspapers?                                              | .. | .. | .. | .. | Y | Y |
| 26 | Has she read any magazines or books?                                               | .. | .. | .. | .. | Y | Y |
| 27 | Has she turned on a radio or television of her own accord?                         | .. | .. | .. | .. | Y | Y |
| 28 | Has she occupied herself with knitting or sewing or any other occupation or hobby? | .. | .. | .. | .. | Y | Y |

question called only for Yes or No. The questionnaire was filled up in the evening and referred to the events of that day only.

As it was thought that the extra attention given to the subjects might induce changes, and in order to be able to eliminate the effects of any secular change as the investigation proceeded, a control group was separated, differing only in that they were given no E.C.T. It was obtained simply as those cases who had been judged suitable for inclusion but whose relatives refused permission for the treatment. We are satisfied that the somewhat unusual method of selection introduced no major bias between the two subgroups.

As might be expected, sedatives could not be entirely withheld during the investigation, but their amounts were small and they were given usually during the night. We followed the rules: (i) give as little as possible; (ii) if some has to

be given, keep the amount as constant as possible throughout the investigation. Records were, of course, kept of the amounts used and on what days they occurred. We are satisfied that the effects were insufficient to introduce major error into the conclusions.

### THE PROCESS

First, each patient was assessed on the measurement scale for three days (Monday, Wednesday and Friday). During the next three weeks she had nine convulsions (three in each week on alternate days). Convulsion was induced by 150V, A.C., square-wave of about 1 second duration, bi-temporally, under thiopentone, with succinylcholine chloride ("Scoline") as relaxant, followed by oxygen. Despite their ages, the patients' physical conditions were not affected adversely by the treatment.

During the week following the last convulsion, the patient was assessed on the measurement scale for three days as before; and a similar three days' measurement was made a month later. Thus the questionnaire was filled in nine times for each patient, a total of 252 questions.

An investigation of this type must not, in fairness to the subjects, be prolonged if its uselessness should become manifest. We watched the results closely, as patient followed patient, and decided to stop after 16 patients had been treated (8 with convulsions and 8 controls). Though this number is very small, we did not feel justified in prolonging the investigation further. The results were then analysed.

### THE RESULTS

From each questionnaire of 28 questions an index of "clinical improvement" was assessed by counting the number of answers (Yes or No) that agreed with the first of the two letters given in Table I. Thus had a patient been marked entirely as shown in the first column, she would have received the maximal marks for Clinical Improvement. (This scoring *defines* how we are using the words "clinical improvement".) As the three forms in one week differed only in factors we were not interested in, the three marks were added together so as to reduce sampling vagaries. Thus each patient gave three scores for Clinical Improvement:

B: Before the convulsions

I: In the week following

II: A month later.

(These symbols will be used in what follows.)

Similarly each questionnaire gave a score for Initiative by counting the number of answers that agree with those marked in the right-hand positions in Table I. (The method of scoring defines what we mean by "initiative".) Thus, for each patient, three scores similar to B, I, and II were formed for Initiative.

The two scales are partly correlated, but not wholly so; for questions 9, 10, 11, 13, 14, 15, and 25 interpret the answer inversely. Thus, to the question "Has she been destructive?" an answer "yes" would imply an increasing activity or initiative, but a clinical deterioration.

The patients' scores for Clinical Improvement and for Initiative are given in Table II.

With our clinical material, we considered that the error would be least if each patient acted as her own control. We were thus interested primarily



TABLE II  
Clinical  
Improvement

| Patient<br>No. | E.C.T. | Clinical<br>Improvement |    |    | Initiative |    |    |
|----------------|--------|-------------------------|----|----|------------|----|----|
|                |        | B                       | I  | II | B          | I  | II |
| 1 .. ..        | +      | 23                      | 25 | 27 | 12         | 16 | 13 |
| 2 .. ..        | +      | 25                      | 24 | 23 | 13         | 16 | 2  |
| 3 .. ..        | +      | 16                      | 18 | 16 | 20         | 9  | 17 |
| 4 .. ..        | +      | 61                      | 36 | 42 | 45         | 27 | 29 |
| 5 .. ..        | +      | 49                      | 29 | 29 | 30         | 13 | 11 |
| 6 .. ..        | +      | 37                      | 25 | 34 | 25         | 10 | 18 |
| 7 .. ..        | +      | 31                      | 45 | 30 | 24         | 30 | 15 |
| 8 .. ..        | +      | 12                      | 18 | 20 | 8          | 7  | 7  |
| 9 .. ..        | —      | 44                      | 46 | 37 | 34         | 38 | 25 |
| 10 .. ..       | —      | 24                      | 22 | 18 | 19         | 17 | 15 |
| 11 .. ..       | —      | 26                      | 28 | 26 | 15         | 14 | 11 |
| 12 .. ..       | —      | 16                      | 19 | 45 | 27         | 8  | 29 |
| 13 .. ..       | —      | 19                      | 18 | 18 | 8          | 11 | 9  |
| 14 .. ..       | —      | 33                      | 35 | 32 | 12         | 22 | 22 |
| 15 .. ..       | —      | 58                      | 55 | 59 | 57         | 53 | 49 |
| 16 .. ..       | —      | 22                      | 22 | 22 | 12         | 11 | 11 |

in how the patient changed from her initial state. We therefore formed, for each patient, on the scores for Clinical Improvement, the differences:

$$d_1 = I - B$$

$$d_2 = II - B$$

$$d_3 = II - I = d_2 - d_1.$$

Similar differences were formed also on the scores for Initiative. The null hypothesis, for testing significance, is that the quantities  $d_i$  are distributed about zero. Each  $d_i$  is based, of course, on the answers to 168 questions.

### *Clinical Improvement*

Taking first the scores for Clinical Improvement, no trend is obvious; and  $t$ -tests for whether  $d_1$ ,  $d_2$ , and  $d_3$  have means displaced from zero show the displacements to be non-significant. Thus there appears to be no uniform tendency for the patients to be improved.

There is a possibility, however, that the patients are being affected individually, some better and some worse, so that the changes do not show on the average. This possibility can be tested by seeing whether the scatter in the scores increases after E.C.T.  $d_1$  is a measure of the immediate response, of how much the patient has been changed; and its variance measures how much the patients have differed in their changes. Taking the corresponding values in the controls as basis for comparison, the variance in  $d_1$  was increased by 37.4 times, which is highly significant ( $P < 0.001$ ,  $n_1 = n_2 = 7$ ).  $d_2$  shows no significant difference, so the effect is evidently not sustained.

This conclusion was clearly supported by clinical observation. Some of the patients were undoubtedly changed for the better, though none to a major degree. Unfortunately, these were balanced by the patients who were influenced unfavourably; on balance, we could not say that any major gain had been achieved. We had the impression that such improvement as there was occurred in the patients whose dementia was simply senile, rather than of the organic or pre-senile type. But the numbers are too small for any confident assertion.

### Initiative

The results above were for Clinical Improvement. Those for Initiative showed that  $d_2$  was significantly depressed ( $0.02 > P > 0.01$ ,  $n=7$ , two-tailed test.) The variances of  $d_1$  and  $d_2$  showed no change. Evidently the treatment was tending, if anything, to depress Initiative.

A number of other tests (on orientation, colour-preferences, reaction-time, etc.) were carried out; but as they showed no significant changes they need not be detailed here.

### DISCUSSION

In its major aim, the investigation has shown that some improvement can be achieved in some cases of senile dementia by the use of E.C.T. On the other hand, some patients are made somewhat worse, and when improvement does occur it is not of major degree. It seems, therefore, when one considers the risks that are inseparable from E.C.T. in its present form, that E.C.T. cannot be recommended as a worthwhile way of improving the condition of the senile patient. If however some substantial modification of E.C.T. is found in the future, that can give E.C.T.'s results without its risks, then the possibility of helping the senile patient in this way should not be forgotten.

But before any question about how E.C.T. should be modified can be answered, we must know more about how it acts. At present, the amount we know about this is practically zero. A minor aim of the investigation was to test, by using cybernetic methods, whether E.C.T. acts simply as a very powerful and non-specific disturber (rather than as a specific alterer of particular variables or parts.) Were this so, the score for Initiative would almost certainly have risen; the fact that the scores for Initiative tended, if anything, to fall suggests fairly strongly that E.C.T. acts through some specialized mechanism rather than as a non-specific disturber.

It is worth noticing that the action of E.C.T. cannot be purely on the factors, whatever they are, that are responsible for depression; for several patients in this series showed distinct improvement though they showed previously no trace of depression. E.C.T. evidently can act on factors other than those responsible for depression. More can hardly be said at the present time.

### SUMMARY

In an attempt to alleviate the inactivity of senility, a selected group was treated with electro-convulsive therapy and measured before and afterwards for the amount of initiative shown and for the degree of clinical improvement. Special scales were constructed so as to make the measurements objective.

A small degree of clinical improvement was shown clearly in some cases but not in all. The simply senile cases responded better than the organic or presenile.

The results were considered from the cybernetic point of view to see if they would throw light on how E.C.T. acts. The evidence suggests that it acts on some specific mechanism rather than as a generalized activator of the whole cortex.

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# THE VALIDITY OF THE MEEHL M.M.P.I. PSYCHOTIC SCALE IN THE DIAGNOSIS OF SCHIZOPHRENIA

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THE detection of early or subclinical schizophrenia is a major psychiatric problem. Patients who are finally classified as schizophrenic often may not have been so considered on previous examination. In other words their true condition was not detected clinically in the first place.

The possibility of reducing such diagnostic errors has been the object of some recent research by Peterson (1956) in which a measure of schizophrenic behaviour was developed and validated. Three groups of patients were used, matched for sex, age, education and intelligence. The experimental group (group 1) consisted of patients whose final diagnosis was schizophrenia but whose initial diagnosis had been different (false negatives). One control group (group 2) consisted of patients who were matched with the experimental group for initial diagnosis but here the diagnosis remained unchanged (true negatives). Another control group (group 3) consisted of latent or "sub-clinical" schizophrenics whose diagnoses were finally confirmed (true positives). Table I summarizes Peterson's groupings.

TABLE I

| Group           | Initial Diagnosis                    | Final Diagnosis | Designation     |
|-----------------|--------------------------------------|-----------------|-----------------|
| 1. Experimental | Other than schizophrenia             | Schizophrenia   | False negatives |
| 2. Control      | Matched with 1                       | Unchanged       | True negatives  |
| 3. Control      | Latent or sub-clinical schizophrenia | Unchanged       | True positives  |

The three groups were compared on a slight modification of the six psychotic signs derived by Meehl (1946) from the M.M.P.I. profile. A statistical comparison showed the frequency of occurrence of each of the six diagnostic signs in group 3 as against group 1. None of the six signs returned a significant chi square. When group 1 was compared with group 2 on the same six signs each one was significant at or beyond the 0.05 level. In addition it was found that when a psychotic score was obtained for any patient in groups 1 and 2 by attributing one mark for the presence of each sign, a cut-off point between



1 and 2 marks would then result in a correct diagnosis of 88 per cent. of the patients previously diagnosed incorrectly. Thirty-nine per cent. of group 2 would then be misclassified.

The present investigation was designed to test the apparent predictive value of this method of classification developed by Peterson.

### METHOD

The sample consisted of 100 consecutive cases whose psychological examination had included the M.M.P.I. Only 91 of these cases were included in the final analysis as there was some doubt about the diagnosis of the remaining 9.

The patients were grouped according to their final psychiatric diagnosis. The groups obtained were 13 schizophrenics, 4 manic-depressive psychotics, 36 dysthymics (reactive depressive, anxiety states and obsessional neurotics), 27 hysterics, 8 behaviour disorders (cases of delinquency and childhood maladjustment), and 3 organics.

The psychotic score from the six signs was obtained for each of the 91 patients and the frequency of occurrence of each score within the diagnostic groups calculated. The significance of the differences of the median scores of every group from every other group was statistically evaluated using the non-parametric median test (Siegel, 1956).

It was considered that if the Meehl signs had predictive validity with respect to cases whose diagnosis was in doubt, then those patients subsequently diagnosed as schizophrenics should be differentiated from those patients of other later diagnoses on the basis of these signs. It was further considered that contamination of the criteria and predictor variables had been avoided in that the Meehl-Peterson signs were not known to us at the time the M.M.P.I. was completed.

### RESULTS

TABLE II

*The Significance of the Differences Between the Diagnostic Groups on Meehl's Signs*

| Groups                           | Manic-depressive Psychoses | Hysterics | Dysthymics | All Neurotics | All Psychotics | Behaviour Disorders | Organics |
|----------------------------------|----------------------------|-----------|------------|---------------|----------------|---------------------|----------|
| Schizophrenics .. ..             | >0.9                       | >0.7      | >0.8       | >0.5          | —              | >0.5                | >0.8     |
| Manic-depressive psychoses .. .. | —                          | >0.5      | >0.3       | >0.5          | —              | >0.1                | >0.2     |
| Hysterics .. ..                  | —                          | —         | >0.2       | —             | >0.8           | >0.2                | >0.2     |
| Dysthymics .. ..                 | —                          | —         | —          | —             | >0.9           | >0.1                | >0.3     |
| All neurotics .. ..              | —                          | —         | —          | —             | >0.5           | >0.2                | >0.2     |
| All psychotics .. ..             | —                          | —         | —          | —             | —              | >0.1                | >0.7     |
| Behaviour disorders .. ..        | —                          | —         | —          | —             | —              | —                   | >0.7     |

No statistically significant differences were obtained between the psychotic scores of any of the groups studied. And least discriminating of all were the differences between the schizophrenic and other groups.

### CONCLUSIONS

Meehl's psychotic signs appear to be of little diagnostic value in the detection of schizophrenia. Peterson's later encouraging results with these signs have not been confirmed. The signs failed to differentiate the schizophrenic group from any of the other diagnostic groups. The significance of the score differences for every other possible comparison between diagnostic groups was equally disappointing. No two nosological groups were differentiated on the basis of the signs.

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# A COMPARISON OF PERPHENAZINE, ('FENTAZIN') SODIUM AMYLOBARBITONE AND A PLACEBO IN ANXIOUS AND DEPRESSED OUT-PATIENTS

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PERPHENAZINE is a phenothiazine derivative, recommended as a tranquillizer (Ayd, 1957; O'Reilly *et al.*, 1957; Goldman, 1958; Preisig and Landman, 1958) and as an anti-emetic (Scurr and Robbie, 1958). The structural formula is 1-(2-hydroxyethyl)-4-3-(2-chloro-10-phenothiazyl)-propyl-piperazine; it has also been called Fentazin and Trilafon. Its action is similar to chlorpromazine, but it is said to be 5 or 6 times as potent, the side-effects are less severe and the potentiating effect on barbiturates is minimal. Extra-pyramidal symptoms have occurred but no serious blood-disorders or jaundice have been reported. The recommended out-patient dosage is 6 to 16 mg. daily; doses of 24 to 64 mg. daily may be used with in-patients. Autonomic side-effects such as blurred vision and dry mouth are said not to occur below 40 mg. daily, hypotension not below 150 mg. daily. The purpose of this trial was to see if perphenazine improved the symptoms of out-patients with anxiety and depression, as compared with a placebo, and also to match it with a recognized and widely used sedative, sodium amylobarbitone, in order to note any difference in effect.

## METHOD

The patients receiving the trial tablets were out-patients with anxiety and depression and were thought suitable for treatment with sedatives or tranquillizers. The 27 subjects, 17 female and 10 male, were of age range 24 to 67 years (mean 36), and their illness had existed for 2 weeks to 7 years (mean 19 months). Fourteen of them had had previous similar illnesses and 4 had been in-patients. On consideration of the relevant factors, 14 were expected to retain some symptoms for many years and 13 were likely to lose all or most of their symptoms.

The tablets prepared for this trial were identical in appearance and taste and were each given four times a day for a fortnight. The perphenazine dose of 2 mg. q.d.s. is a moderately low dose suitable as an initial amount for out-patients. One grain of sodium amylobarbitone q.d.s. was arbitrarily chosen as a moderately low dose that might have comparable effects without a high incidence of somnolence. The placebo was lactose. The hospital pharmacist allotted the six possible sequences of the three treatments to the patients in random order. The doctor did not know which treatment the patient was having at any given period until the end of the trial. He told the patient he was giving the tablets to see if they helped. The patient attended weekly or fortnightly for half-hour interviews during the six weeks. The effect of the treatment was assessed by the patient and the doctor separately, each using two methods. Firstly, the patient rated each symptom by underlining the relevant degree of severity on the form shown. For anxiety, depression, phobias



## FORM USED FOR PATIENT'S ASSESSMENT OF OWN SYMPTOMS

Name .....

Fortnight ending .....

Please underline the word you think most suitable in describing your feelings in the last two weeks.

In general I have felt:

Well; Slightly unwell; Mildly unwell; Moderately unwell; Very unwell.

Feelings of *panic* have been:

Absent; Slight; Mild; Moderate; Severe.

Feelings of *being miserable* have been:

Absent; Slight; Mild; Moderate; Severe.

My appetite has been:

Good; Quite good; Fair; Poor; Very poor.

Dislike or fear of *being shut in* has been:

Absent; Slight; Mild; Moderate; Severe.

Symptoms of *headache* have been:

Absent; Slight; Mild; Moderate; Severe.

My sleep has been:

Good; Quite good; Fair; Poor; Very poor.

Have you noticed any unwanted effects of the pills in the last two weeks?.....

Any other comment.....

Rating .....

and somatic complaints the form was filled in with the word initially used by the patient when the history was taken. The questions concerning general well-being, appetite and sleep were common to all. The patients also noted any side-effects of the tablets and made any other comments applicable. Secondly, at the end of the trial, the patient was asked to rank in order of preference the three fortnights of treatment. Thirdly, the doctor assessed the degree of anxiety and of depression present in the patient during each fortnight, judging by the clinical appearance and the discussion during the interviews. Anxiety and depression were rated as absent, slight, mild, moderate or severe (0-4). "Severe" was not often used, as sustained severe anxiety or depression usually warrants the patient entering hospital. In assessing anxiety such features as unease, panic, fears for the future, agitated movements, voluble speech or anxious silences were taken into account, and for depression the loss of interest and pleasure, impaired effort, misery, decreased activity and spontaneity. Fourthly, the doctor ranked the three fortnights of treatment according to the degree of improvement. Any environmental change liable to alter the patient's state was noted for each fortnight. Failure to take all the tablets was probably discovered as the patient was asked to return the container and any tablets left over. The same doctor made all the observations.

## RESULTS

The 27 patients each completed the trial, taking the different tablets for the three fortnights. One other patient had to leave the trial after three weeks as she was admitted to hospital and her place in the sequence was filled by another patient.

*Doctor's Assessment of Mental State*

The anxiety and depression of the patient were each rated 0-4 (absent-severe), the maximum possible score would be 8. The initial and the three fortnightly scores were compared (Table I). A 2-way Analysis of Variance was performed and it was shown that the means for treatment differed very significantly ( $V.R.=11.23$ ,  $P<.01$ ). Then the means of treatments were

TABLE I

*Mean Score for Doctor's Assessment of Anxiety and Depression*

| Before Treatment | Perphenazine | Sodium<br>Amylobarbitone | Placebo |
|------------------|--------------|--------------------------|---------|
| 4.40             | 2.52         | 3.00                     | 3.40    |

compared in pairs using the "Multiple Range Test" (Duncan, 1955) and the differences were again significant at the 1 per cent. level. Perphenazine and sodium amylobarbitone improved the patient more than placebo and, in the doses used, perphenazine was more effective than sodium amylobarbitone. In order to see if the treatments had any selective effect on anxiety or depression, the proportion of the patients improved were compared, i.e. those patients whose anxiety or depression was less following a fortnight's treatment. As it may be seen from the percentage improving in Table II, whereas perphenazine

TABLE II

*Proportion of Patients Improving (Doctor's Assessment)*

|                 |    | Perphenazine<br>(Per cent.) | Sodium<br>Amylobarbitone<br>(Per cent.) | Placebo<br>(Per cent.) |
|-----------------|----|-----------------------------|-----------------------------------------|------------------------|
| Depression less | .. | 63                          | 26                                      | 29                     |
| Anxiety less    | .. | 67                          | 62                                      | 41                     |

decreased the symptoms of depression to a significant degree, sodium amylobarbitone was not any more effective than placebo in this respect. (Using the arc sin transformation of the square roots of the proportions, as described by Davies (1954), the critical ratio was 2.4 and the difference significant at the 2 per cent. level.) Relief of anxiety was achieved by both to a similar extent.

*Patients' Assessment of Own Symptoms*

As described above, each of the patient's symptoms was rated 0-4, giving a possible score of 28. Using the 2-way Analysis of Variance again, the effect of treatment was shown to be highly significant, as is shown in Table III ( $V.R.=9.49$ ,  $P<.01$ ). With these results, however, there was no significant

TABLE III

*Mean Score for Patients' Assessment of Own Symptoms*

| Before Treatment | Perphenazine | Sodium<br>Amylobarbitone | Placebo |
|------------------|--------------|--------------------------|---------|
| 18.35            | 13.10        | 13.32                    | 14.47   |

difference between the treatments employed. The same trend was demonstrated if individual symptoms were considered. The tendency throughout is for greater improvement on the active drugs but this is only present to a significant

degree for appetite, which increased more with perphenazine than sodium amylobarbitone and placebo (arc sin  $\sqrt{p}$  method, C.R.=2.2,  $P<0.05$ ).

### Ranking Order of Benefit

The patients' and doctor's ratings are considered together because, although the ranking order for the same subject was sometimes different, the overall results show considerable agreement (2 patients could not decide between the 2nd and 3rd). A  $\chi^2$  test was performed on the two results shown in Table IV

TABLE IV  
*Ranking Order of Preference of Treatments by Patient and Doctor*

|                       | Patients |        |       | Doctor |        |       |
|-----------------------|----------|--------|-------|--------|--------|-------|
|                       | First    | Second | Third | First  | Second | Third |
| Perphenazine .. .. .  | 14       | 5      | 7     | 15     | 5      | 7     |
| Sodium amylobarbitone | 9        | 11     | 5     | 9      | 10     | 8     |
| Placebo .. .. .       | 4        | 9      | 13    | 3      | 12     | 12    |

and both were significant at the 2 per cent. level ( $\chi^2=11.85$  and  $12.44$ ). Again, both drugs were more effective than placebo and, with the dosage used, perphenazine was the more beneficial.

Significant environmental change recorded during any fortnight's treatment fell randomly and would not appear to affect the results. Changes such as a new job, mother going into hospital, husband returning after a period of absence were accepted as significant and happened 4 times whilst the patient was receiving sodium amylobarbitone and 3 times each with perphenazine and placebo.

The majority of patients appeared to have taken the tablets regularly. In 9 out of the 81 fortnights of treatment a few tablets were returned, although never as many as a quarter of the total. Concerning those returned, it was usually said that the tablets were not helping and hence were easily forgotten. It occurred once with perphenazine, thrice with sodium amylobarbitone and five times with placebo.

No serious side-effects were encountered throughout the trial. Symptoms possibly due to the treatment were recorded, the outstanding one being some initial sleepiness in six patients receiving sodium amylobarbitone. The following symptoms were reported once each; headache, tinnitus and constipation whilst taking perphenazine; depression, nausea, dry tongue, numbness and puffy hands and face whilst receiving sodium amylobarbitone and depression and constipation with placebo.

### DISCUSSION

The effect of perphenazine and sodium amylobarbitone is best assessed in comparison with patients receiving the same form of treatment but taking a placebo, although a placebo has its own peculiar effects (Lasagna *et al.*, 1958). The mental state tends to improve with the passage of time, the visits to the hospital, the interviews with the doctor and the taking of some tablets. On this programme approximately 40 per cent. of these patients improved during the fortnight on placebo; by the end of the six weeks about 75 per cent. of the patients had improved to varying degrees. Statistical analysis has shown that a significantly greater improvement takes place during administration of perphenazine and sodium amylobarbitone. This result was obtained from



three of the four methods used to assess the treatment, viz. the doctor's rating of mental state during the trial, the patients' and the doctor's ranking the order of benefit during the three fortnights of treatment whilst the contents of the tablets were unknown to them. The patients' assessment of their own symptoms appeared to be a cruder measure. They sometimes commented on how difficult it was to apply any standard of severity to their own symptoms. The results of their completion of the form for symptoms showed significant benefit during the six weeks of treatment but failed to differentiate to a significant degree between treatments. Reliance upon patients rating their own symptoms or assessing their own improvement can be ill-founded, as is often evident in clinical practice. Patients are more successful in comparing the efficacy of the two drugs; in this trial the patients' ranking of the drugs' effectiveness agreed closely with the doctor's ranking and his assessment of change in their mental state. Estimating changes which are largely subjective increases the difficulties in trials of drugs (Beecher, 1952); this experiment was designed to avoid some of the hazards. The rating scales in psychiatry (Lorr, 1954) did not appear to be applicable to the symptoms studied and so the present form for patients was devised. Its success was limited.

This trial compares the effectiveness of perphenazine and sodium amylobarbitone only at one dosage. Both, in the rather low dosage employed, have a significant and comparable beneficial action upon anxiety. There is a significant difference between their respective effects on depression; sodium amylobarbitone was no more effective than the control tablets, whereas perphenazine was. Ayd (1957), however, thought that perphenazine had little or no effect upon endogenous depression. Perphenazine is said to have less toxic effects than chlorpromazine. The final answer to this claim can only come from wider use of this phenothiazine derivative. In this trial there were no serious side-effects. Some symptoms attributed to the drug treatment by the patient might well have been due to their mental illness, except drowsiness in a few patients on sodium amylobarbitone.

#### SUMMARY

A controlled trial of perphenazine 8 mg. daily, sodium amylobarbitone 4 gr. daily and a placebo, each being given in random sequence for two weeks to anxious or depressed out-patients, is described.

The patients improved more with perphenazine and sodium amylobarbitone than with placebo, the difference being statistically highly significant.

At the dosage employed, perphenazine and sodium amylobarbitone had an equal effect on anxiety. Perphenazine improved depression significantly but sodium amylobarbitone was no more effective than placebo in this respect.

No serious side-effects or toxic actions were encountered during the trial.

The difficulty of measuring changes in the patient's mental state is discussed. The doctor's fortnightly rating of anxiety and depression, the patients' and the doctor's ranking order of benefit for the three kinds of medication gave the same highly significant result. The patients' own assessment of symptoms showed the trend less well.

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